(72) Inventors:
 • **van der Vossen, Edwin Andries Gerard**
 3572 ZM Utrecht (NL)
 • **Allefs, Josephus Jacobus Hendricus Maria**
 8304 EJ Emmeloord (NL)

(74) Representative: **Prins, Adrianus Willem et al**
Vereenigde,
Nieuwe Parklaan 97
2587 BN Den Haag (NL)

Remarks:
The sequence listing, which is published as annex to the application documents, was filed after the date of filing. The applicant has declared that it does not include matter which goes beyond the content of the application as filed.

(54)   **Gene conferring resistance to Phytophthera infestans (late-blight) in Solanaceae**

(57)   The invention relates to the field of plant diseases, in particular to oomycete infections such as late blight, a disease of major importance to production of *Solanacae* such as potato and tomato cultivars. The invention provides a method for providing a plant or its progeny with resistance against an oomycete infection comprising providing said plant or part thereof with a gene or functional fragment thereof comprising a nucleic acid, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* with resistance against an oomycete fungus.

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Description

[0001]   The invention relates to the field of plant diseases.

[0002]   Late blight, caused by the oomycete pathogen *Phytophthora infestans* is world-wide the most destructive disease for potato cultivation. The disease also threatens the tomato crop. The urgency of obtaining resistant cultivars has intensified as more virulent, crop-specialised and pesticide resistant strains of the pathogen are rapidly emerging.

[0003]   A way to prevent crop failures or reduced yields is the application of fungicides that prevent or cure an infection by *P. infestans*. However, the application of crop protectants is widely considered to be a burden for the environment. Thus, in several Western countries, legislation is becoming more restrictive and partly prohibitive to the application of specific fungicides, making chemical control of the disease more difficult. An alternative approach is the use of cultivars that harbour partial or complete resistance to late blight. Two types of resistance to late blight have been described and used in potato breeding. One kind is conferred by a series of major, dominant genes that render the host incompatible with specific races of the pathogen (race specific resistance). Eleven such *R* genes (*R1-R11*) have been identified and are believed to have originated in the wild potato species *Solanum demissum*, which is native to Mexico, where the greatest genetic variation of the pathogen is found. Several of these *R* genes have been mapped on the genetic map of potato. *R1* and *R2* are located on chromosomes 5 and 4, respectively. *R3, R6* and *R7* are located on chromosome 11. Unknown *R* genes conferring race specific resistance to late blight have also been described in *S. tuberosum* ssp. *andigena* and *S. berthaultii*. Because of the high level of resistance and ease of transfer, many cultivars contain *S. demissum* derived resistance. Unfortunately, *S. demissum* derived race specific resistance, although nearly complete, is not durable. Once newly bred cultivars are grown on larger scale in commercial fields, new virulences emerge in *P. infestans* that render the pathogen able to overcome the introgressed resistance. The second type of resistance, often quantitative in nature, is race non-specific and is thought to be more durable. Race non-specific resistance to late blight can be found in several Mexican and Middle and South American *Solanum* species.

[0004]   Diploid *S. bulbocastanum* from Mexico and Guatemala is one of the tuber bearing species that is known for its race non-specific resistance to late blight. Despite differences in endosperm balance numbers, introgression of the *S. bulbocastanum* resistance trait has been successful. Ploidy manipulations and a series of tedious bridge crosses has resulted in *S. bulbocastanum* derived, *P. infestans* resistant germplasm. However, almost 40 years after the first crosses and intense and continuous breeding efforts by potato breeders in the Netherlands with this germplasm, late blight resistant cultivars still remain to be introduced on the market. Successful production of somatic hybrids of *S. bulbocastanum* and *S. tuberosum* has also been reported. Some of these hybrids and backcrossed germplasm were found to be highly resistant to late blight, even under extreme disease pressure. Despite reports of suppression of recombination, resistance in the backcrossed material appeared to be on chromosome 8 within an approximately 6 cM interval between the RFLP markers CP53 and CT64. A CAPS marker derived from the tomato RFLP probe CT88 cosegregated with resistance. Suppression of recombination between the *S. bulbocastanum* and *S. tuberosum* chromosomes forms a potential obstacle for successful reconstitution of the recurrent cultivated potato germplasm to a level that could meet the standards for newly bred potato cultivars. Isolation of the genes that code for resistance found in *S. bulbocastanum* and subsequent transformation of existing cultivars with these genes, would be a much more straight forward and quicker approach when compared to introgression breeding.

[0005]   The cloning and molecular characterisation of numerous plant *R* genes conferring disease resistance to bacteria, fungi, viruses, nematodes, and insects has identified several structural features characteristic to plant *R* genes. The majority are members of tightly linked multigene families and all *R* genes characterised so far, with the exception of Pto, encode leucine-rich repeats (LRRs), structures shown to be involved in protein-protein interactions. LRR containing *R* genes can be divided into two classes based on the presence of a putative tripartite nucleotide-binding site (NBS). *R* genes of the NBS-LRR class comprise motifs that are shared with animal apoptosis regulatory proteins. The second class of LRR containing *R* genes encompasses genes with a predicted hydrophobic membrane-anchoring domain with a predicted extracellular N-terminal LRR motif. The recently cloned resistance gene *R1* conferring race specific resistance to late blight belongs to the NBS-LRR class of *R* genes.

[0006]   The invention provides an isolated or recombinant nucleic acid essentially corresponding to a cluster of genes identifiable by phylogenetic tree analyses, preferably of the encoded amino acid sequence, for example when comparing functionalities, as corresponding to the *Rpi-blb, RGC1-blb, RGC3-blb* and *RGC4-blb* gene cluster (herein also called the *Rpi-blb* gene cluster) of figure 9.

[0007]   Phylogenetic tree analysis is carried out as follows. First a multiple sequence alignment is made of the nucleic acid sequences an/or preferably of the deduced amino acid sequences of the genes to be analysed using CLUSTALW (http://www2.ebi.ac.uk/clustalw), which is in standard use in the art. ClustalW produces a .dnd file, which can be read by TREEVIEW (http://taxonomy.zoology.gla.ac.uk/rod/rod.html). The phylogenetic tree depicted in Figure 9 is a phylogram.

[0008]   Phylogenetic studies of the deduced amino acid sequences of *Rpi-blb, RGC1-blb, RGC3-blb, RGC4-blb* and those of the most similar genes from the art (as defined by the BLASTX) derived from diverse species, using the

Neighbour-Joining method of Saitou and Nei (1987), shows that corresponding genes or functional fragments thereof of the *Rpi-blb* gene cluster can be placed in a separate branch (Figure 9).

[0009]   Sequence comparisons between the four members of the *Rpi-blb* gene cluster identified on 8005-8 BAC clone SPB4 show that sequence homology within the *Rpi-blb* gene cluster varies between 70% and 81% at the amino acid sequence level, providing a convenient rule of thumb: a nucleic acid encoding a peptide of at least 15 amino acids, preferably of at least 25 amino acids, most preferably of at least 50 amino acids, having at least 70% homology to corresponding stretches of peptides selected from any of the proteins encoded by the *Rpi-blb, RGC1-blb, RGC3-blb* and *RGC4-blb* genes are provided as functional fragment, herewith. The deduced amino acid sequence of *Rpi-blb* shares the highest overall homology with *RGC3-blb* (81% amino-acid sequence identity; Table 4). When the different domains are compared it is clear that the effector domains present in the N-terminal halves of the proteins (coiled-coil and NBS-ARC domains) share a higher degree of homology (91% sequence identity) than the C-terminal halves of these proteins which are thought to contain the recognition domains (LRRs; 71% amino acid sequence identity). Comparison of all four amino-acid sequences revealed a total of 104 Rpi-blb specific amino acid residues (Figure 10). The majority of these are located in the LRR region (80/104). Within the latter region, these specific residues are concentrated in the LRR subdomain xxLxLxxxx. The relative frequency of these specific amino-acid residues within this LRR subdomain is more than two times higher (28.3%) than that observed in the rest of the LRR domain (12.3%). The residues positioned around the two conserved leucine residues in the consensus xxLxxLxxxx are thought to be solvent exposed and are therefore likely to be involved in creating/maintaining recognition specificity of the resistance protein.

[0010]   Sequences of additional members of the *Rpi-blb* gene cluster can be obtained by screening genomic DNA or insert libraries, e.g. BAC libraries with primers based on signature sequences of the *Rpi-blb* gene. Screening of various *Solanum* BAC libraries with primer sets A and/or B (Table 2 and Figure 7) identified numerous *Rpi-blb* homologues derived from different *Solanum* species. Alignment of these additional sequences with those presented in Figure 10 will help identify additional members of the *Rpi-blb* gene cluster and specific amino acid residues therein responsible for *P. infestans* resistance specificity. Furthermore, testing additional sequences in the above described phylogenetic tree analyses, e.g. using the Neighbour-Joining method of Saitou and Nei (1987), provides additional identification of genes belonging to the *Rpi-blb* gene cluster.

[0011]   The invention provides the development of an intraspecific mapping population of *S. bulbocastanum* that segregated for race non-specific resistance to late blight. The resistance was mapped on chromosome 8, in a region located 0.3 cM distal from CT88. Due to the race non-specific nature of the resistance, *S. bulbocastanum* late blight resistance has always been thought to be *R* gene independent. However, with the current invention we demonstrate for the first time that *S. bulbocastanum* race non-specific resistance is in fact conferred by a gene bearing similarity to an *R* gene of the NBS-LRR type.

[0012]   The invention further provides the molecular analysis of this genomic region and the isolation by map-based cloning of a DNA-fragment of the resistant parent that harbours an *R* gene, designated *Rpi-blb*. This DNA-fragment was subcloned from an approximately 80 kb bacterial artificial chromosome (BAC) clone which contained four complete *R* gene-like sequences in a cluster-like arrangement. Transformation of a susceptible potato cultivar by *Agrobacterium tumefaciens* revealed that one of the four *R* gene-like sequences corresponds to *Rpi-blb* that provides the race non-specific resistance to late blight. Characterisation of the *Rpi-blb* gene showed that it is a member of the NBS-LRR class of plant *R* genes. The closest functionally characterised sequences of the prior art are members of the *I2* resistance gene family in tomato. These sequences have an overall amino acid sequence identity of approximately 32% with that of *Rpi-blb*.

[0013]   Thus, in a first embodiment, the invention provides an isolated or recombinant nucleic acid, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with race non-specific resistance against an oomycete pathogen.

[0014]   Isolation of the gene as provided here that codes for the desired resistance trait against late blight and subsequent transformation of existing potato and tomato cultivars with this gene now provides a much more straightforward and quicker approach when compared to introgression breeding. The results provided here offer possibilities to further study the molecular basis of the plant pathogen interaction, the ecological role of *R* genes in a wild Mexican potato species and are useful for development of resistant potato or tomato cultivars by means of genetic modification.

[0015]   In contrast to the *R* genes cloned and described so far, the gene we provide here is the first isolated *R* gene from a *Solanum* species that provides race non-specific resistance against an oomycete pathogen. Notably, the invention provides here a nucleic acid wherein said *Solanum* species that is provided with the desired resistance comprises *S. tuberosum*. In particular, it is the first gene that has been isolated from a phylogenetically distinct relative of cultivated potato, *S. bulbocastanum*, for which it was shown by complementation assays, that it is functional in *S. tuberosum*. These data imply that the gene *Rpi-blb* can easily be applied in potato production without a need for time-consuming and complex introgression breeding.

[0016]   The following definitions are provided for terms used in the description and examples that follow.

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- *Nucleic acid:* a double or single stranded DNA or RNA molecule.
- *Oligonucleotide:* a short single-stranded nucleic acid molecule.
- *Primer:* the term primer refers to an oligonucleotide that can prime the synthesis of nucleic acid.
- *Homology:* homology may be defined and determined by the TBLASTN or TBLASTP program for nucleic acid or amino acid sequences, respectively, of Altschul *et al.* (1990), which is in standard use in the art, or, and this may be preferred, the standard program BestFit, which is part of the Wisconsin Package, Version 8, September 1994, (Genetics Computer Group, 575 Science Drive, Madison, Wisconsin, USA, Wisconsin 53711). Homology may be at the nucleotide sequence and/or encoded amino acid sequence level. Preferably the nucleic acid and/or amino acid sequence shares at least 50%, or 60% homology, most preferably at least about 70%, or 80% or 90% homology with the sequence as depicted in Fig. 6. As shown in Table 4, the closest functionally characterised sequence of the prior art (members of the *I2 Fusarium* resistance gene cluster in tomato) has a much lower level of amino acid sequence identity than this (32% with respect to that of *Rpi-blb*). Homology within the *R* gene cluster of the present invention varies between 70% and 81% at the amino acid sequence level. Alternatively, a sequence is defined as belonging to the same cluster when numerous sequences are compared according to the Neighbour-Joining method of Saitou and Nei (1987).
- *Promoter:* the term "promoter" is intended to mean a short DNA sequence to which RNA polymerase and/or other transcription initiation factors bind prior to transcription of the DNA to which the promoter is functionally connected, allowing transcription to take place. The promoter is usually situated upstream (5') of the coding sequence. In its broader scope, the term "promoter" includes the RNA polymerase binding site as well as regulatory sequence elements located within several hundreds of base pairs, occasionally even further away, from the transcription start site. Such regulatory sequences are, e.g., sequences that are involved in the binding of protein factors that control the effectiveness of transcription initiation in response to physiological conditions. The promoter region should be functional in the host cell and preferably corresponds to the natural promoter region of the *Rpi-blb* resistance gene. However, any heterologous promoter region can be used as long as it is functional in the host cell where expression is desired. The heterologous promoter can be either constitutive or regulatable. A constitutive promoter such as the CaMV 35S promoter or T-DNA promoters, all well known to those skilled in the art, is a promoter which is subjected to substantially no regulation such as induction or repression, but which allows for a steady and substantially unchanged transcription of the DNA sequence to which it is functionally bound in all active cells of the organism provided that other requirements for the transcription to take place is fulfilled. A regulatable promoter is a promoter of which the function is regulated by one or more factors. These factors may either be such which by their presence ensure expression of the relevant DNA sequence or may, alternatively, be such which suppress the expression of the DNA sequence so that their absence causes the DNA sequence to be expressed. Thus, the promoter and optionally its associated regulatory sequence may be activated by the presence or absence of one or more factors to affect transcription of the DNA sequences of the genetic construct of the invention. Suitable promoter sequences and means for obtaining an increased transcription and expression are known to those skilled in the art.
- *Terminator:* the transcription terminator serves to terminate the transcription of the DNA into RNA and is preferably selected from the group consisting of plant transcription terminator sequences, bacterial transcription terminator sequences and plant virus terminator sequences known to those skilled in the art.
- *Gene:* the term "gene" is used to indicate a DNA sequence which is involved in producing a polypeptide chain and which includes regions preceding and following the coding region (5'-upstream and 3'-downstream sequences) as well as intervening sequences, the so-called introns, which are placed between individual coding segments (so-called exons) or in the 5'-upstream or 3'-downstream region. The 5'-upstream region may comprise a regulatory sequence that controls the expression of the gene, typically a promoter. The 3'-downstream region may comprise sequences which are involved in termination of transcription of the gene and optionally sequences responsible for polyadenylation of the transcript and the 3' untranslated region. The term "resistance gene" is an isolated nucleic acid according to the invention said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete pathogen, said nucleic acid preferably comprising a sequence as depicted in Fig. 6 or part thereof, or a homologous sequence with essentially similar functional and structural characteristics. A functionally equivalent fragment of such a resistance gene or nucleic acid as provided by the invention encodes a fragment of a polypeptide having an amino acid sequence as depicted in Fig. 8 or part thereof, or a homologous and/or functionally equivalent polypeptide, said fragment exhibiting the characteristic of providing at least partial resistance to an oomycete infection such as caused by *P. infestans* when incorporated and expressed in a plant or plant cell.
- *Resistance gene product:* a polypeptide having an amino acid sequence as depicted in Fig. 8 or part thereof, or a homologous and/or functionally equivalent polypeptide exhibiting the characteristic of providing at least partial resistance to an oomycete infection such as caused by *P. infestans* when incorporated and expressed in a plant or plant cell.

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- R₀ plant: primary regenerant from a transformation experiment, also denoted as transformed plant or transgenic plant.

[0017] In the present invention we have identified and isolated the resistance gene *Rpi-blb*, which confers race non-specific resistance to *Phytophthora infestans*. The gene was cloned from a *Solanum bulbocastanum* genotype that is resistant to *P. infestans*. The isolated resistance gene according to the invention can be transferred to a susceptible host plant using *Agrobacterium* mediated transformation or any other known transformation method, and is involved in conferring the host plant resistant to plant pathogens, especially *P. infestans*. The host plant can be potato, tomato or any other plant, in particular a member of the *Solanacae* family that may be infected by such a plant pathogen. The present invention provides also a nucleic acid sequence comprising the *Rpi-blb* gene, or a functionally equivalent fragment thereof, which is depicted in Figure 6.

[0018] With the *Rpi-blb* resistance gene or functionally equivalent fragment thereof according to the invention, one has an effective means of control against plant pathogens, since the gene can be used for transforming susceptible plant genotypes thereby producing genetically transformed plants having a reduced susceptibility or being preferably resistant to a plant pathogen. In particular, a plant genetically transformed with the *Rpiblb* resistance gene according to the invention has a reduced susceptibility to *P. infestans*.

[0019] In a preferred embodiment the *Rpi-blb* resistance gene comprises the coding sequence provided in Figure 6B or any corresponding or homologous sequence preceded by a promoter region and/or followed by a terminator region. The promoter region should be functional in plant cells, and preferably correspond to the native promoter region of the *Rpi-blb* gene. However, a heterologous promoter region that is functional in plant cells can be used in conjunction with the coding sequences.

[0020] In addition the invention relates to the *Rpi-blb* resistance gene product which is encoded by the *Rpi-blb* gene according to the invention and which has an amino acid sequence provided in Figure 8, or which is homologous to the deduced amino acid sequence or part thereof.

[0021] The invention also provides a vector comprising a nucleic acid as provided herein, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete pathogen, or a functionally equivalent isolated or recombinant nucleic acid in particular wherein said member comprises *S. tuberosum* or *Lycopersicon esculentum*.

[0022] The invention also provides a host cell comprising a nucleic acid or a vector according to the invention. An example of said host cell is provided in the detailed description herein. In a particular embodiment, said host cell comprises a plant cell. As a plant cell a cell derived from a member of the *Solanacae* family is preferred, in particular wherein said member comprises *S. tuberosum* or *Lycopersicon esculentum*. From such a cell, or protoplast, a transgenic plant, such as transgenic potato plant or tomato plant with resistance against an oomycete infection can arise. The invention thus also provides a plant, or tuber root, fruit or seed or part or progeny derived thereof comprising a cell according to the invention.

[0023] Furthermore, the invention provides a proteinaceous substance, exhibiting the characteristic of providing at least partial resistance to an oomycete infection such as caused by *P. infestans* when incorporated and expressed in a plant or plant cell. In particular such a proteinaceous substance is provided that is encoded by a nucleic acid according to the invention. In a preferred embodiment, the invention provides a proteinaceous substance comprising an amino acid sequence as depicted in figure 8 or part thereof. Such a proteinaceous substance is for example useful for obtaining a binding molecule directed at said substance. Particular easy to obtain, merely by immunizing an appropriate animal and harvesting a polyclonal serum or a monoclonal antibody, are antibodies or fragments thereof, but other binding molecules such as synthetic antibodies or peptide mimics thereof can for example be obtained by phage display methods.

[0024] Furthermore, the invention provides a binding molecule directed at a nucleic acid according to the invention. For example, the *Rpi-blb* gene can be used for the design of oligonucleotides complementary to one strand of the DNA sequence as depicted in Figure 7 and Table 2. Such oligonucleotides as provided herein are useful as probes for library screening, hybridisation probes for Southern/Northern analysis, primers for PCR, for use in a diagnostic kit for the detection of disease resistance and so on. Such oligonucleotides are useful fragments of an isolated or recombinant nucleic acid as provided herein, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete fungus, or a functionally equivalent isolated or recombinant nucleic acid, in particular wherein said member comprises *S. tuberosum* or *Lycopersicon esculentum*. They can be easily selected from a sequence as depicted in figure 6 or part thereof. A particular point of recognition comprises the LRR domain as identified herein. Such a binding molecule according to the invention is used as a probe or primer, for example provided with a label, in particular wherein said label comprises an excitable moiety which makes it useful to detect the presence of said binding molecule.

[0025] The invention furthermore provides a method for selecting a plant or plant material or progeny thereof for its susceptibility or resistance to an oomycete infection comprising testing at least part of said plant or plant material or

progeny thereof for the presence or absence of a nucleic acid, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete fungus, or for the presence of said gene product, said method preferably comprising contacting at least part of said plant or plant material or progeny thereof with a binding molecule according the invention and determining the binding of said molecule to said part. Said method is particularly useful wherein said oomycete comprises *P. infestans*, allowing to select plants or planting material for resistance against late blight, for example wherein said plant or material comprises *S. tuberosum*.

[0026] Also, the invention provides use of a nucleic acid or a vector or a cell or a substance or a binding molecule according to the invention in a method for providing a plant or its progeny with at least partial resistance against an oomycete infection, in particular wherein said oomycete comprises *P. infestans* especially wherein said plant comprises *S. tuberosum*, said method for providing a plant or its progeny with at least partial resistance against an oomycete infection comprising providing said plant or part thereof with a gene or functional fragment thereof comprising a nucleic acid, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete fungus, or providing said plant or part thereof with a nucleic acid or a vector or a cell or a substance according to the invention.

[0027] Furthermore, the invention provides an isolated *S. bulbocastanum*, or part thereof, such as a tuber or seed, susceptible to an oomycete infection caused by *P. infestans*.

[0028] The invention is further described in the detailed description below.

DESCRIPTION OF THE FIGURES

[0029]

Figure 1. Geographical map of Mexico indicating the origin of *Solanum bulbocastanum* accessions used to isolate the *Rpi-blb* gene. The letters a, b and c indicate the relative geographical origins of the used *S. bulbocastanum* accessions.

Figure 2. Genetic linkage maps of the *Rpi-blb* locus on chromosome 8 of *S. bulbocastanum*. Horizontal lines indicate the relative positions of markers linked to late blight resistance. Distances between markers are indicated in centimorgans. A. Genetic position of the. *Rpi-blb* locus relative to markers TG513, CT88 and CT64 (n=508 genotypes). B. High density genetic linkage map of the *Rpi-blb* locus (n=2109 genotypes).

Figure 3. Physical map of the *Rpiblb* locus. A. Genetic and physical map of the *S. bulbocastanum* genomic region containing *Rpi*blb1. Vertical arrows indicate the relative positions of markers linked to resistance. Numbers above the horizontal line indicate the number of recombinants identified between the flanking markers in 2109 progeny plants. Rectangles represent bacterial artificial chromosome (BAC) clones. B. Relative positions of candidate genes for late blight resistance on BAC SPB4. C. Schematic representation of the *Rpi-blb* gene structure. Horizontal lines indicate exons. Open boxes represent coding sequence. Lines angled downwards indicate the position of a 678-nucleotide long intron sequence.

Figure 4. Southern blot analysis of the BAC contig spanning the *Rpi-blb* locus. Names above each lane represent the names of BAC clones. The names of the restriction enzymes used to digest the BAC DNA prior to Southern blotting are indicated.

Figure 5. Detached leaf disease assays. A. Resistant (left), intermediate (centre) and susceptible (right) phenotypes found in the *S. bulbocastanum* mapping population B8 6 days post inoculation (d.p.i) with *P. infestans* sporangiospore droplets. B. Genetic complementation for late blight resistance. Characteristic disease phenotypes of leaves derived from transgenic potato plants harbouring *RGC1-blb*, *RGC2-blb*, *-blb* or *RGC4-blb* 6 d.p.i. with *P. infestans* sporangiospore droplets. Genetic constructs harbouring the RGCs were transferred to the susceptible potato cultivar Impala through *Agrobacterium* mediated transformation.

Figure 6. Nucleic acid sequences of the *Rpi-blb* gene cluster members. A. Coding nucleic acid sequence of the *Rpi-blb* gene. B. Coding nucleic acid sequence of the *Rpi-blb* gene including the intron sequence (position 428-1106). C. Sequence of the 7.35 kb *Sau3AI* genomic DNA fragment of *S. bulbocastanum* BAC SPB4 present in pRGC2-blb, the genetic construct used for genetic complementation for late blight resistance. The genetic construct harbours the *Rpi-blb* gene. The initiation codon (ATG position 2648-2650) and the termination codon (TAA position 6237-6239) are underlined. D. Coding nucleic acid sequence of *RGC1-blb* including the intron sequence (position 428-708). E. Coding nucleic acid sequence of *RGC3-blb* including the intron sequence (position 428-1458). F. Coding nucleic acid sequence of *RGC4-blb* including intron sequences (positions 434-510, 543-618

and 743-1365).

Figure 7. Relative primer positions. The horizontal bar represents the coding sequence of the *Rpi-blb* gene. Numbers represent nucleotide positions. Horizontal arrows indicate relative primer positions and orientations. GSP1 and GSP2 represent nested gene specific primers used for 3' RACE experiments. GSP3 and GSP4 represent nested gene specific primers used for 5' RACE experiments. A(F), A(R), B(F) and B(R) are primers used to amplify *Rpi-blb* homologues. The position of the restriction site *NsiI* used to make domain swaps between *Rpi-blb* homologues is indicated.

Figure 8. Deduced Rpi-blb protein sequence. The amino acid sequence deduced from the DNA sequence of *Rpi-blb* is divided into three domains (A-C), as described in the text. Hydrophobic residues in domain A that form the first and fourth residues of heptad repeats of potential coiled-coil domains are underlined. Conserved motifs in R proteins are written in lowercase and in italic in domain B. Residues matching the consensus of the cytoplasmic LRR are indicated in bold in domain C. Dots in the sequence have been introduced to align the sequence to the consensus LRR sequence of cytoplasmic LRRs.

Figure 9. Phylogenetic tree of state of the art sequences which share some homology to the deduced amino acid sequence of *Rpi-blb* and its gene cluster members *RGC1-blb, RGC3-blb* and *RGC4-blb*. The tree was made according to the Neighbour-Joining method of Saitou and Nei (1987). An asterix indicates that the gene has been assigned a function. The *Rpi-blb* gene cluster is boxed.

Figure 10. Alignment of the deduced protein products encoded by *Rpi-blb, RGC1-blb, RGC3-blb* and *RGC4-blb*. The complete amino acid sequence of Rpi-blb is shown and amino acid residues from RGC1-blb, RGC3-blb and RGC4-blb that differ from the corresponding residue in Rpi-blb. Dashes indicate gaps inserted to maintain optimal alignment. Amino acid residues that are specific for Rpi-blb, when compared to those at corresponding positions in RGC1-blb, RGC3-blb and RGC4-blb, are highlighted in bold. The regions of the LRRs that correspond to the consensus L..L..L..C/N/S..a..aP are underlined. Conserved motifs in the NBS domain are indicated in lowercase.

Figure 11. Schematic overview of domain swaps made between *Rpi-blb* and homologues *RGC1-blb* and *RGC3-blb*. The vertical dotted line indicates the position of the *NsiI* site used to make the swaps. R and S indicate whether transgenic plants harbouring specific chimeric constructs are resistant or susceptible to late blight infection, respectively.

Detailed description

[0030] For the mapping of the *Rpi-blb* resistance gene an intraspecific mapping population of *S. bulbocastanum* was developed. A crucial step in this process was the identification of susceptible *S. bulbocastanum* genotypes. For this purpose several *S. bulbocastanum* accessions originating from different clusters/areas in Mexico were analysed for *P. infestans* resistance or susceptibility in a detached leaf assay (Table 1 and Figure 1). The screened accessions BGRC 8008 and BGRC 7999 contained no susceptible genotypes. However in the accessions BGRC 8005, BGRC 8006 and BGRC 7997, susceptibility was found in 9%, 7% and 14 % of the analysed seedlings, respectively. A *P. infestans* susceptible clone of accession BGRC 8006 was subsequently selected and crossed with a resistant clone of accession BGRC 8005. The resulting F1 population was used to map the *Rpi-blb* locus and is hereafter referred to as the B8 population.

[0031] Initial screening of 42 B8 genotypes for resistance to *P. infestans* in a detached leaf assay suggested that *P. infestans* resistance in *S. bulbocastanum* accession 8005 could be caused by a single dominant *R* gene, or a tightly linked gene cluster. Of the 42 genotypes tested, 22 scored resistant and 16 susceptible in a repeated experiment. Resistance phenotypes of the remaining 4 seedlings remained unclear. In order to determine the chromosome position of this *S. bulbocastanum* resistance, B8 genotypes with an undoubted phenotype were used for marker analysis. The chromosome 8 specific marker TG330 (Table 2) was found to be linked in repulsion phase with the resistant phenotype, as only one recombinant was obtained between this marker and resistance in 12 B8 genotypes. Furthermore, chromosome 8 marker CT88 (Table 2) was found to be completely linked in repulsion phase to resistance, indicating that the locus responsible for resistance, designated *Rpi-blb*, was located in this region of chromosome 8. For this reason, tomato chromosome 8 specific markers that map proximal and distal to CT88 (TG513 and CT64; Tanksley et al., 1992; Table 2) were developed into CAPS markers and tested in 512 B8 genotypes with known resistance phenotypes. A total of five CT64-CT88 recombinant genotypes and 41 CT88-TG513 recombinant genotypes were identified in this screen (Figure 2A). The resistance locus *Rpi-blb* was mapped 1 recombination event distal to marker CT88 (Figure 2A).

[0032] Fine mapping of the *Rpi-blb* locus was carried out with CAPS markers derived from left (L) and right (R) border

sequences of BAC clones isolated from a BAC library prepared from the resistant *S. bulbocastanum* genotype BGRC 8005-8. The BAC library was initially screened with markers CT88 and CT64. BAC clones identified with these markers were used as seed BACs for a subsequent chromosome walk to the *Rpi-blb* locus. A total of 2109 B8 genotypes were screened for recombination between markers TG513 en CT64. All recombinant genotypes (219/2109) were subsequently screened with all available markers in the CT88-CT64 genetic interval. These data together with the disease resistance data of each recombinant, obtained through detached leaf assays, positioned the *Rpi-blb* locus between markers SPB33L and B149R, a 0.1 cM genetic interval (4/2109 recombinants) physically spanned by the overlapping BAC clones SPB4 and B49 (Figures 2b and 3). Within this interval resistance cosegregated with the BAC end marker SPB42L, the sequence of which shared homology to the *Fusarium I2* gene cluster from tomato (Ori et al., 1997, Simons et al., 1998). Southern analyses of BAC clones spanning the SP33L-B149R interval using a ^{32}P-labeled PCR fragment of marker SPB42L as a probe revealed the presence of at least 4 copies of this *R* gene like sequence within the *Rpi-blb* interval (Figure 4). Moreover, all of these copies were present on BAC SPB4. Sequencing and annotation of the complete insert of this BAC clone indeed identified four complete *R* gene candidates (*RGC1-blb, RGC2-blb, RGC3-blb and RGC4-blb*) of the NBS-LRR class of plant *R* genes. A PCR-marker that was located in-between *RGC1-blb* and *RGC4-blb* revealed recombination between *P. infestans* resistance and *RGC4-blb*, ruling out the possibility of *RGC4-blb* being *Rpi-blb*. Despite this finding, all four RGCs were selected for complementation analysis.

[0033]   Genomic fragments of approximately 10 kb harbouring *RGC1-blb, RGC2-blb, RGC3-blb* or *RGC4-blb* were subcloned from BAC SPB4 into the binary plant transformation vector pBINPLUS (van Engelen et al., 1995) and transferred to a susceptible potato cultivar using standard transformation methods. Primary transformants were tested for *P. infestans* resistance as described in Example 1. Only the genetic construct harbouring *RGC2-blb* was able to complement the susceptible phenotype; 86% of the R$_0$(*RGC2-blb*) plants were resistant (Table 3) whereas all *RGC1-blb, RGC3-blb* and *RGC4-blb* containing primary transformants were completely susceptible to *P. infestans*. The resistant *RGC2-blb* containingtransformants showed similar resistance phenotypes as the *S. bulbocastanum* resistant parent (Figure 5). *RGC2-blb* was therefore designated the *Rpi-blb* gene, the DNA sequence of which is provided in Figure 6.

EXAMPLE 1: DISEASE ASSAY

[0034]   The phenotype of *S. bulbocastanum* and transgenic *S. tuberosum* genotypes for resistance to *P. infestans* was determined by detached leaf assays. Leaves from plants grown for 6 to 12 weeks in the greenhouse were placed in pieces of water-saturated florists foam, approximately 35x4x4 cm, and put in a tray (40 cm width, 60 cm length and 6 cm height) with a perforated bottom. Each leaf was inoculated with two droplets or more (25 μl each) of sporanglospore solution on the abaxial side. Subsequently, the tray was placed in a plastic bag on top of a tray, in which a water-saturated filter paper was placed, and incubated in a climate room at 17°C and a 16h/8h day/night photoperiod with fluorescent light (Philips TLD50W/84HF). After 6 days, the leaves were evaluated for the development of *P. infestans* disease symptoms. Plants with leaves that clearly showed sporulating lesions 6 days after inoculation were considered to have a susceptible phenotype whereas plants with leaves showing no visible symptoms or necrosis at the side of inoculation in the absence of clear sporulation were considered to be resistant. The assay was performed with *P. infestans* complex isolate 655-2A, which was obtained from Plant Research International BV (Wageningen, The Netherlands).

EXAMPLE 2: MAPPING OF THE *Rpi-blb* RESISTANCE LOCUS

Plant material

[0035]   In order to produce an intraspecific mapping population that segregated for the *P. infestans* resistance gene present in *S. bulbocastanum* accession BGRC 8005 (CGN 17692, PI 275193), a susceptible *S. bulbocastanum* genotype was required. Several *S. bulbocastanum* accessions originating from different clusters/areas in Mexico were analysed for *P. infestans* resistance or susceptibility in a detached leaf assay (Table 1 and Figure 1). In accession BGRC 8008 and BGRC 7999 no susceptibility was detected. In accession BGRC 8005, BGRC 8006 and BGRC 7997 susceptibility was only present in 9%, 7% and 14 % of the analysed seedlings, respectively. Thus, only a few susceptible *S. bulbocastanum* genotypes were obtained.

[0036]   The intraspecific mapping population of S. *bulbocastanum* (B8) was produced by crossing a *P. infestans* susceptible clone of accession BGRC 8006 with a resistant clone of accession BGRC 8005. DNA of 2109 progeny plants was extracted from young leaves according to Doyle and Doyle (1989).

CAPS marker analysis

[0037]   For PCR analysis, 15 μl reaction mixtures were prepared containing 0.5 μg DNA, 15 ng of each primer, 0.2

mM of each dNTP, 0.6 units Taq-polymerase (15 U/μl, SphaeroQ, Leiden, The Netherlands), 10 mM Tris-HCl pH 9, 1.5 mM MgCl₂, 50 mM KCl, 0.1% Triton X-100 and 0.01% (w/v) gelatin. The PCRs were performed using the following cycle profile: 25 seconds DNA denaturation at 94°C, 30 seconds annealing (see Table 1) and 40 seconds elongation at 72°C. As a first step in PCR-amplification DNA was denatured for 5 min at 94°C and finalised by an extra 5 min elongation step at 72°C. The amplification reactions were performed in a Biometra® T-Gradient or Biometra® Uno-II thermocycler (Westburg, Leusden, The Netherlands). Depending on the marker, the PCR product was digested with an appropriate restriction enzyme. An overview of the markers including primer sequences, annealing temperature and restriction enzymes, is given in Table 2. Subsequently, the (digested) PCR products were analysed by electrophoresis in agarose or acrylamide gels. For acrylamide gel analysis, the CleanGel DNA Analysis Kit and DNA Silver Staining Kit (Amersham Pharmacia Biotech Benelux, Roosendaal, the Netherlands) were used.

Genetic mapping of the *Rpi-blb* locus

[0038] Initially a small group of 42 progeny plants of the B8 population was screened for resistance to *P. infestans* in a detached leaf assay. Plants with leaves that clearly showed sporulating lesions 6 days after inoculation were considered to have a susceptible phenotype whereas plants with leaves showing no visible symptoms or necrosis at the side of inoculation in the absence of clear sporulation were considered to be resistant. Of the 42 seedlings, 22 scored resistant and 16 susceptible. The phenotype of the remaining 4 seedlings remained unclear in this initial phase. These data indicated that resistance could be due to a single dominant gene or a tightly linked gene cluster. In order to determine the chromosome position, seedlings with a reliable phenotype were used for marker analysis. Chromosome 8 marker TG330 was found to be linked in repulsion with the resistant phenotype, as only one recombinant was obtained between this marker and resistance in 12 B8 seedlings. Furthermore, chromosome 8 marker CT88 was found to be completely linked in repulsion phase to resistance, indicating that a resistance gene was located on chromosome 8.

[0039] Subsequently, chromosome 8 specific markers that had been mapped proximal and distal to CT88 (Tanksley et al., 1992) were developed to CAPS markers. In order to map these markers more precisely, another 512 individuals of the B8 population were screened for late blight resistance using the detached leaf disease assay. Simultaneously, plants were scored for the markers CT64, CT88 and TG513. For 5 seedlings, recombination was detected between markers CT64 and CT88, while 41 seedlings were recombinant between markers CT88 and TG513 (Figure 2A). The resistance gene *Rpi-blb* was mapped in between markers CT64 and CT88. In this stage, the positioning of CT88 proximal to *Rpi-blb* was based on only one recombined seedling.
[0040] In order to determine the position of *Rpi-blb* more precisely relative to the available markers, another 1555 seedlings of the B8 population were grown and analysed for recombination between the markers TG513 and CT64. Thus, a total of 2109 individual offspring clones of the B8 population were screened. Recombination between markers TG513 en CT64 was detected in 219 of these seedlings (10.4 cM). All of the recombinants were screened with marker CT88 and phenotyped for the resistance trait by making use of the detached leaf assay. In agreement with earlier results, the *Rpi-blb* gene was mapped in between markers CT88 and CT64 (Figure 2B).

EXAMPLE 3: CONSTRUCTION OF A *S. BULBOCASTANUM* BAC LIBRARY AND CONSTRUCTION OF A CONTIGUOUS BAC CONTIG SPANNING THE *Rpi-blb* LOCUS

BAC library construction

[0041] A resistant clone of *S. bulbocastanum* (blb) accession BGRC 8005 (CGN 17692, PI 275193) heterozygous for the *Rpi-blb* locus, was used as source DNA for the construction of a genomic BAC library, hereafter referred to as the 8005-8 BAC library. High molecular weight DNA preparation and BAC library construction were carried out as described in Rouppe van der Voort et al. (1999). Approximately 130.000 clones with an average insert size of 100 kb, which corresponds to 15 genome equivalents were finally obtained. A total of approximately 83.000 individual clones were stored in 216 384-well microtiter plates (Invitrogen, The Netherlands) containing LB freezing buffer (36 mM K₂HPO₄, 13.2 mM KH₂PO₄, 1.7 mM citrate, 0.4 mM MgSO₄, 6.8 mM (NH₄)₂SO₄, 4.4 % V/V glycerol, 12.5 μg/ml chloramphenicol in LB medium) at -80°C. Another 50.000 clones were stored as bacterial pools containing ∼1000 white colonies. These were generated by scraping the colonies from the agar plates into LB medium containing 18% glycerol and 12.5 μg/ml chloramphenicol using a sterile glass spreader. These so-called super pools were also stored at -80°C.

Screening of the BAC library and construction of a physical map of the *Rpi-blb* locus

[0042] The 8005-8 BAC library was initially screened with CAPS markers CT88 and CT64. This was carried out as

follows. For the first part of the library of approximately 83.000 clones stored in 384 well microtiter plates, plasmid DNA was isolated using the standard alkaline lysis protocol (Sambrook et al., 1989) from pooled bacteria of each plate to produce 216 plate pools. To identify individual BAC clones carrying the CAPS markers the plate pools were screened by PCR. Once an individual plate pool was identified as being positive for a particular CAPS marker the positive row and positive column were identified through a two dimensional PCR screening. For this purpose, the mother 384-well plate was replicated twice on LB medium containing chloramphenicol (12.5 µg/ml). After growing the colonies for 16 h at 37°C one plate was used to scrape the 24 colonies of each row together and the other plate was used to scrape the 16 colonies of each column together. Bacteria of each row or column were resuspended in 200 µl TE buffer. CAPS marker analysis on 5 µl of these bacterial suspensions was subsequently carried out leading to the identification of single positive BAC clones. For the second part of the library, stored as 50 pools of approximately 1000 clones, plasmid DNA was isolated from each pool of clones using the standard alkaline lysis protocol and PCR was carried out to identify positive pools. Bacteria corresponding to positive pools were diluted and plated on LB agar plates containing chloramphenicol (12.5 µg/ml). Individual white colonies were subsequently picked into 384-well microtiter plates and single positive BAC clones subsequently identified as described above. Names of BAC clones isolated from the super pools carry the prefix SP (e.g. SPB33).

[0043] Insert sizes of BAC clones were estimated as follows. Positive BAC clones were analysed by isolating plasmid DNA from 2 ml overnight cultures (LB medium supplemented with 12.5 mg/ml chloramphenicol) using the standard alkaline lysis miniprep protocol and resuspended in 20 µl TE. Plasmid DNA (10 µl) was digested with 5 U NotI for 3 h at 37°C to free the genomic DNA from the pBeloBAC11 vector. The digested DNA was separated by CHEF electrophoresis in a 1% agarose gel in 0.5 X TBE at 4°C using a BIORAD CHEF DR II system (Bio-Rad Laboratories, USA) at 150 volts with a constant pulse time of 14 sec for 16 h.

[0044] Screening of the 8005-8 BAC library with marker CT88 identified two positive BAC clones: B139 and B180, with potato DNA inserts of 130 and 120 kb, respectively (Figure 3A). Digestion of the CT88 PCR product generated from these BAC clones and several resistant and susceptible progeny plants of the B8 mapping population with MboI revealed that BAC139 carried the CT88 allele that was linked in cis to resistance. To identify the relative genome position of BAC B139, pairs of PCR primers were designed based on the sequence of the right (R) and left (L) ends of the insert. BAC end sequencing was carried out as described in Example 4 using 0.5 µg of BAC DNA as template. Polymorphic CAPS markers were developed by digesting the PCR products of the two parent genotypes of the B8 population and of two resistant and two susceptible progeny genotypes with several 4-base cutting restriction enzymes (Table 2). Screening of the 37 CT88-CT64 recombinant B8 genotypes mapped 5 of the 7 CT88-Rpi-blb recombinants between CT88 and B139R, indicating that marker B139R was relatively closer to the Rpi-blb locus than marker CT88. Screening of the 216 plate pools with B139R did not lead to the identification of a positive BAC clone. Screening of the 50 super pools identified the positive BAC clones SPB33 and SPB42 with DNA inserts of 85 and 75 kb, respectively (Figure 3A). Screening of the complete BAC library with SPB33L identified the positive BAC clones B149 and SPB4. BAC clone SPB4 contained the SPB33L allele that was linked in cis to resistance whereas BAC clone B149 did not. However, screening of the CT88-CT64 recombinant panel with B149R revealed that this BAC spanned the Rpi-blb locus. B149R was separated from the Rpi-blb locus by two recombination events (Figure 3A). Screening of the 8005-8 BAC library with B149R identified BAC clone B49 as having the B149R allele that was linked in cis to resistance. This BAC clone together with BAC clone SPB4 therefore formed a BAC contig that spanned the Rpi-blb locus (Figure 3).

EXAMPLE 4: SEQUENCE ANALYSIS OF BAC SPB4 AND IDENTIFICATION OF RESISTANCE GENE CANDIDATES WITHIN THE Rpi-blb LOCUS

[0045] Within the SPB33L-B149R interval resistance cosegregated with BAC end marker SPB42L, the sequence of which shared homology to NBS-LRR genes of the Fusarium I2 gene cluster in tomato (Ori et al., 1997; Simons et al., 1998). Southern analyses of BAC clones spanning the SPB33L-B149R interval using a ^{32}P-labeled PCR fragment of marker SPB42L as a probe revealed the presence of at least 4 copies of this R gene like sequence within the Rpi-blb interval (Figure 4). Moreover, all of these copies were present on BAC SPB4. The DNA sequence of BAC clone SPB4 was therefore determined by shotgun sequence analysis. A set of random subclones with an average insert size of 1.5 kb was generated. 10 µg of CsCl purified DNA was sheared for 6 seconds on ice at 6 amplitude microns in 200 µl TE using an MSE soniprep 150 sonicator. After ethanol precipitation and resuspension in 20 µl TE the ends of the DNA fragments were repaired by T4 DNA polymerase incubation at 11°C for 25 minutes in a 50 µl reaction mixture comprising 1x T4 DNA polymerase buffer (New England BioLabs, USA), 1 mM DTT, 100 µM of all 4 dNTP's and 25 U T4 DNA polymerase (New England Biolabs, USA), followed by incubation at 65°C for 15 minutes. The sheared DNA was subsequently separated by electrophoresis on 1% SeaPlaque LMP agarose gel (FMC). The fraction with a size of 1.5-2.5 kb was excised from the gel and dialysed against 50 ml TE for 2 hr at 4°C. Dialysed agarose slices were then transferred to a 1.5 ml Eppendorf tube, melted at 70°C for 5 min, digested with 1 unit of GELASE (Epicentre Technologies, USA) per 100 mg of agarose gel for 1 hr at 45°C, and the DNA was subsequently precipitated. The 1.5-2.5 kb fragments

were ligated at 16°C in a *EcoRV* restricted and dephosphorylated pBluescript SK⁺ vector (Stratagene Inc.). The ligation mixture was subsequently used to transform ElectroMAX *E. coli* DH10B competent cells (Life Technologies, UK) by electroporation using the BioRad Gene Pulser. Settings on the BioRad Gene Pulser were as recommended for *E. coli* by the manufacturer. The cells were spread on Luria broth (LB) agar plates containing ampicillin (100 μg/ml), 5-bromo-4-chloro-3-indolyl-β-D-galactoside (Xgal) (64 μg/ml) and isopropyl-1-thio-β-D-galactoside (IPTG) (32 μg/ml). Plates were incubated at 37°C for 24 hours. Individual white colonies were grown in 96-well flat-bottom blocks (1.5 ml Terrific Broth medium containing 100 μg/ml ampicillin).

[0046]   Plasmid DNA was isolated using the QIAprep 96 Turbo Miniprep system in conjunction with the BioRobot™ 9600 (QIAGEN) according to the manufacturers instructions. Sequencing reactions were performed using ABI PRISM BigDye™ Terminator cycle sequencing kit (Stratagene) according to the manufacturer's instructions. All clones were sequenced bi-directionally using universal primers. Sequence products were separated by capillary electrophoresis on a Perkin Elmer ABI 3700 DNA Analyzer.

[0047]   The automated assembly of the shotgun reads was carried out using the Phred-Phrap programs (Ewing and Green, 1998; Ewing *et al.*, 1998). A total of 835 reads provided an overall BAC sequence coverage equal to 5x. Gaps between contigs were closed by primer walking or through a combinatorial PCR approach. The sequence was finally edited at Phred quality 40 (1 error every 10,000 nt) by manual inspection of the assembly using the Gap4 contig editor and re-sequencing of all low-quality regions. The complete sequence of the insert of BAC SPB4 consisted of 77,283 nucleotides.

[0048]   Analysis of the contiguous sequence of BAC SPB4 using the computer programme GENSCAN (Burge and Karlin, 1997), GENEMARK (Lukashin and Borodovsky, 1998) and BLASTX (Altschul *et al.*, 1990) identified four complete *R* gene candidate sequences (*RGC1-blb, RGC2-blb, RGC3-blb and RGC4-blb*) belonging to the NBS-LRR class of plant *R* genes. A CAPS marker designed in between *RGC1-blb* and *RGC4-blb*, marker RGC1-4 revealed recombination between *P. infestans* resistance and *RGC4-blb*, ruling out the possibility of *RGC4-blb* being *Rpi-blb* (Figure 3A and B). Despite this finding, all four RGCs were selected for complementation analysis.

EXAMPLE 5: COMPLEMENTATION ANALYSIS

Subcloning of candidate genes and transformation to *Agrobacterium tumefaciens*

[0049]   Genomic fragments of approximately 10 kb harbouring *RGC1-blb, RGC2-blb, RGC3-blb or RGC4-blb* were subcloned from BAC clone SPB4 into the binary plant transformation vector pBINPLUS (van Engelen et al., 1995). Restriction enzyme digestion of BAC clone SPB4 DNA and subsequent size selection was carried out as follows. Aliquots of ~1 μg DNA were digested with 1U, 0.1U or 0.01U of *Sau3*AI restriction enzym for 30 min. The partially digested BAC DNA was subjected to CHEF electrophoresis at 4°C in 0.5 X TBE using a linear increasing pulse time of 1-10 sec and a field strength of 6 V/cm for 16 hr. After electrophoresis, the agarose gel was stained with ethidium bromide to locate the region of the gel containing DNA fragments of approximately 10kb in size. This region was excised from the gel using a glass coverslip and dialysed against 50 ml TE for 2 hr at 4°C. Dialysed agarose slices were then transferred to a 1.5 ml Eppendorf tube, melted at 70°C for 5 min and digested with 1 unit of GELASE (Epicentre Technologies, USA) per 100 mg of agarose gel for 1 hr at 45°C. Ligation of the size selected DNA to *Bam*HI-digested and dephosphorylated pBINPLUS and subsequent transformation of ElectroMAX *E. coli* DH10B competent cells (Life Technologies, UK) with the ligated DNA was carried as described in Example 5, using the BioRad Gene Pulser for electroporation. The cells were spread on Luria broth (LB) agar plates containing kanamycin (50 μg/ml), Xgal (64 μg/ml) and IPTG (32 μg/ml). Plates were incubated at 37°C for 24 hours. Individual white colonies were grown in 96-well plates (100 μl LB medium containing 50 μg/ml kanamycin). A total of 480 clones were PCR screened for the presence of RGCs using primers SPB42LF and SPB42LR or RGC4F and RGC4R (Table 2.). Positive clones were selected for plasmid isolation and further characterisation. Identification of clones harbouring *RGC1-blb, RGC2-blb, RGC3-blb or RGC4-blb* was carried out by sequencing the SPB42L PCR fragments derived from positive clones. The relative position of the RGCs within a subclone was determined by sequencing the ends of the clone and subsequent comparison of the sequences to the complete BAC insert sequence. Finally four binary plasmids, pRGC1-blb, pRGC2-blb, pRGC3-blb and pRGC4-blb were selected and transferred to *Agrobacterium tumefaciens* strains AGL0 (Lazo *et al.*, 1991), LBA4404 (Hoekema *et al.*, 1983) or UIA143 (Farrand *et al.*, 1989) either by electroporation using the BioRad Gene Pulser or by conjugation. Settings on the BioRad Gene Pulser were as recommended for A. *tumefaciens* by the manufacturer. Conjugation was carried out as described by Simon *et al.* (1983). The cells were spread on Luria broth (LB) agar plates containing kanamycin (100 mg/l) and rifampicin (50 mg/l). Plates were incubated at 28°C for 48 hours. Small-scale cultures from selected colonies were grown in LB medium containing kanamycin (100 mg/l) and rifampicin (50 mg/l). Plasmid DNA was isolated as described previously and the integrity of the plasmids was verified by restriction analysis upon reisolation from A. *tumefaciens* and subsequent transformation to *E. coli*. A *tumefaciens* cultures harbouring a plasmid with the correct DNA pattern were used to transform a susceptible potato genotype.

Transformation of susceptible potato cultivar

[0050] A. tumefaciens strains were grown for 2 days at 28°C in 20 ml LB medium supplemented with 50 mg/l rifampicine and 25 mg/l kanamycin. Subsequently, 0.2 ml of A. tumefaciens culture was diluted in 10 ml LB medium containing the same antibiotics and grown overnight (28°C). The overnight culture was centrifuged (30 min, 2647 x g) and the pellet was resuspended in 50 ml MS medium (Murashige and Skoog, 1962) supplemented with 30 g/l sucrose (MS30).

[0051] Certified seed potatoes of cultivar Impala were peeled and surface sterilised for 30 min. in a 1% sodium hypochlorate solution containing 0.1 % Tween-20. Tubers were then washed thoroughly in large volumes of sterile distilled water (4 times, 10 min). Discs of approximately 2 mm thickness and 7 mm in diameter, were sliced from cylinders of tuber tissue prepared with a corkborer. The tuber discs were transferred into liquid MS30 medium containing A. tumefaciens and incubated for 15 min. After removing the A. tumefaciens solution, the tuber discs were transferred to regeneration medium containing MS30, 0.9 mg/l IAA, 3.6 mg/l zeatine riboside and 8 g/l agar (Hoekema et al., 1989). The plates were incubated at 24°C, 16 hour day-length (Philips TLD50W/84HF). After 48 hours of co-cultivation, the tuber discs were rinsed for 5 min in liquid MS medium including antibiotics, 200 mg/l vancomycin, 250 mg/l cefotaxim and 75 mg/l kanamycin, and transferred to regeneration medium supplemented with the same antibiotics. The plates were incubated at 24°C, 16 hour day-length (Philips TLD50W/84HF). Every three weeks, the tuber discs were transferred to fresh medium. Regenerating shoots were transferred to MS30 medium containing 75 mg/l kanamycin. Rooting shoots were propagated in vitro and tested for absence of A. tumefaciens cells by incubating a piece of stem in 3 ml LB medium (3 weeks, 37°C, 400 rpm). One plant of each transformed regenerant was transferred to the greenhouse.

Complementation of the susceptible phenotype in potato

[0052] Primary transformants were tested for P. infestans resistance as described in Example 1. Only the genetic construct harbouring RGC2-blb was able to complement the susceptible phenotype; 86% of the R_0RGC2-blb plants were resistant (Table 3) whereas all RGC1-blb, RGC3-blb and RGC4-blb containing primary transformants were completely susceptible to P. infestans. The resistant RGC2-blb transformants showed similar resistance phenotypes as the S. bulbocastanum resistant parent (Figure 5). RGC2-blb was therefore designated the Rpi-blb gene, the DNA sequence of which is provided in Figure 6.

Transformation of susceptible tomato

[0053] Seeds of the susceptible tomato line Moneymaker were rinsed in 70% ethanol to dissolve the seed coat and washed with sterile water. Subsequently, the seeds were surface-sterilised in 1.5% sodium hypochlorite for 15 minutes, rinsed three times in sterile water and placed in containers containing 140 ml MS medium pH 6.0 (Murashige and Skoog, 1962) supplemented with 10 g/l sucrose (MS10) and 160 ml vermiculite. The seeds were left to germinate for 8 days at 25°C and 0.5 W/M² light. Eight day old cotyledon explants were pre-cultured for 24 hours in Petri dishes containing a two week old feeder layer of tobacco suspension cells plated on co-cultivation medium (MS30 pH 5.8 supplemented with Nitsch vitamines (Duchefa Biochemie BV, Haarlem, The Netherlands), 0.5 g/l MES buffer and 8 g/l Daichin agar).

[0054] Overnight cultures of A. tumefaciens were centrifuged and the pellet was resuspended in cell suspension medium (MS30 pH 5.8 supplemented with Nitsch vitamines, 0.5 g/l MES buffer, pH 5.8) containing 200 µM acetosyringone to a final O.D.$_{600}$ of 0.25. The explants were then infected with the diluted overnight culture of A. tumefaciens strain UIA143 (Farrand et al., 1989) containing the helper plasmid pCH32 (Hamilton et al., 1996) and pRGC2-blb for 25 minutes, blotted dry on sterile filter paper and co-cultured for 48 hours on the original feeder layer plates. Culture conditions were as described above.

[0055] Following the co-cultivation, the cotyledons explants were transferred to Petri dishes with selective shoot inducing medium (MS pH 5.8 supplemented with 10 g/l glucose, including Nitsch vitamines, 0.5 g/l MES buffer, 5 g/l agargel, 2 mg/l zeatine riboside, 400 mg/l carbenicilline, 100 mg/l kanamycine, 0.1 mg/l IAA) and cultured at 25°C with 3-5 W/m² light. The explants were sub-cultured every 3 weeks onto fresh medium. Emerging shoots were dissected from the underlying callus and transferred to containers with selective root inducing medium (MS10 pH 5.8 supplemented with Nitsch vitamines, 0.5 g/l MES buffer, 5 g/l agargel, 0.25 mg/l IBA, 200 mg/l carbenicillin and 100 mg/l kanamycine).

Complementation of the susceptible phenotype in tomato

[0056] Primary transformants were tested for P. infestans resistance essentially as described in Example 1 for potato leaves, except that a P. infestans isolate was used that is specific for tomato. The tomato isolate was obtained from Plant Research International BV (Wageningen, The Netherlands). In total 10 transformants containing an intact

RGC2-blb construct were tested for resistance to *P. infestans.* The disease resistance assay revealed that *Rpi-blb* is able to complement a susceptible tomato phenotype.

Molecular analysis of primary transformants

RT-PCR analysis

[0057] In order to produce cDNA, a mix of 19 µl containing 1 µg of total or polyA RNA, 0.25 mM of each dNTP, 50 mM Tris-HCl pH 8.3, 75 mM KCl, 3 mM MgCl$_2$, 10 mM DTT and 530 ng oligo d(T) primer, GCTGTCAACGA-TACGCTACGTAACGGCATGACAGTG(T)$_{18}$ was denatured (1 min 83°C). Subsequently, the mix was placed at 42°C and 1 µl reverse transcriptase (M-MLV reverse transcriptase, Promega Benelux b.v., Leiden, The Netherlands) was added. After 60 min, the mix was heated for 1 min at 99°C and transferred to ice. 2 µl cDNA was used for standard PCR.

Rapid amplification of cDNA ends

[0058] The 5' and 3' ends of the *Rpi-blb* cDNA were determined by rapid amplification of cDNA ends (RACE) using the GeneRacer™ kit (Invitrogen™, The Netherlands). 3' RACE was carried out with the primers GSP1 (5'-GAGGAATC-CATCTCCCAGAG) and GSP2 (5'-GTGCTTGAAGAGATGATAATTCACGAG) in combination with the GeneRacer™ 3' primer and GeneRacer™ 3' nested primer. 5' RACE was carried out on cDNA synthesised with the primer GSP3 (5'-GTCCATCTCACCAAGTAGTGG) using primers GSP4 (5'-GAAATGCTCAGTAACTCTCTGG) and GSP5 (5'-GGAG-GACTGAAAGGTGTTGG) in combination with the GeneRacer™ 5' primer and GeneRacer™ 5' nested primer (Figure 7).

EXAMPLE 6: STRUCTURE OF THE *Rpi-blb* GENE AND THE CORRESPONDING PROTEIN.

[0059] The size and structure of the *Rpi-blb* gene was determined by comparing the genomic sequence derived from the insert of pRGC2-blb with cDNA fragments generated by 5' and 3' rapid amplification of cDNA ends. RACE identified 5' and 3' *Rpi-blb* specific cDNA fragments of a single species, respectively, suggesting that the genomic clone encodes a single *Rpi-blb* specific transcript. The coding sequence of the *Rpi-blb* transcript is estimated to be 2910 nucleotides (nt). The *Rpi-blb* gene contains a single intron of 678 nt starting 428 nt after the translational ATG start codon of the gene (Figure 3C).

[0060] The deduced open reading frame of the *Rpi-blb* gene encodes a predicted polypeptide of 970 amino acids with an estimated molecular weight of 110.3 kD (Figure 8). Several functional motifs present in *R* genes of the NBS-LRR class of plant R genes are apparent in the encoded protein which can be subdivided into 3 domains (A, B and C; Figure 8). The N-terminal part of the protein contains potential coiled-coil domains, heptad repeats in which the first and fourth residues are generally hydrophobic (domain A). Domain B harbours the NBS and other motifs that constitute the NB-ARC domain (ARC for Apaf-1, R protein, and CED-4) of R proteins and cell death regulators in animals (van der Biezen and Jones, 1998). This domain includes the Ap-ATPase motifs present in proteins of eukaryotic and prokaryotic origin (Aravind et *al.,* 1999). The C-terminal half of Rpi-blb comprises a series of 20 irregular LRRs (domain C). The LRRs can be aligned according to the consensus sequence LxxLxxLxLxxC/N/SxxLxxLPxxa, where x designates any residue and "a" designates the positions of aliphatic amino acids, followed by a region of varying length. This repeat format approximates the consensus for cytoplasmic LRRs (Jones and Jones, 1997).

EXAMPLE 7: NATURAL HOMOLOGUES AND ARTIFICIAL VARIANTS OF THE *Rpi-blb* GENE

Natural homologues

[0061] BLASTX homology searches with the coding sequence of the *Rpi-blb* gene revealed that amino acid sequence homology with various state of the art genes does not exceed 36% sequence identity (Table 4). The best BLASTX score was obtained with an NBS-LRR gene derived from *Oryza saliva* (36% amino acid sequence identity). NBS-LRR genes sharing an overall sequence homology of 27-36% amino-acid sequence identity with *Rpi-blb* can be found among others in *Arabidopsis thaliana, Phaseolus vulgaris, Lycopersicon esculentum (Fusarium I2* gene cluster; Ori et al., 1997; Simons et al, 1998), *Zea mays, Hordeum vulgare* and *Lactuca sativa.* Phylogenetic studies of the deduced amino acid sequences of *Rpi-blb, RGC1-blb, RGC3-blb, RGC4-blb* and those of the most homologous state of the art genes (as defined by BLASTX) derived from diverse species, using the Neighbour-Joining method of Saitou and Nei (1987), shows that members of the *Rpi-blb* gene cluster can be placed in a separate branch (Figure 9).

[0062] Sequence comparisons of the four R gene candidates identified on 8005-8 BAC clone SPB4 show that sequence homology within the *Rpi-blb* gene cluster varies between 70% and 81% at the amino acid sequence level. The

deduced amino acid sequence of *Rpiblb* shares the highest overall homology with *RGC3-blb* (81% amino acid sequence identity; Table 4). When the different domains are compared it is clear that the putative effector domains present in the N-terminal halves of the proteins (coiled-coil and NB-ARC domains) share a higher degree of homology (91% amino acid sequence identity) than the C-terminal halves of these proteins which are thought to contain the recognition domains (LRRs; 71% amino acid sequence identity). Comparison of all four amino acid sequences revealed a total of 104 Rpi-blb specific amino acid residues (Figure 10). The majority of these are located in the LRR region (80/104). Within the latter region, these specific residues are concentrated in the LRR subdomain xxLxLxxxx. The relative frequency of these specific amino-acid residues within this LRR subdomain is more than two times higher (28.3%) than that observed in the rest of the LRR domain (12.3%). The residues positioned around the two conserved leucine residues in the consensus xxLxxLxxxx are thought to be solvent exposed and are therefore likely to be involved in creating/maintaining recognition specificity of the resistance protein.

[0063] Sequences of additional homologues of the *Rpi-blb* gene can be obtained by screening genomic DNA or insert libraries, e.g. BAC libraries with primers based on signature sequences of the *Rpi-blb* gene. Screening of various *Solanum* BAC libraries with primer sets A and/or B (Table 2 and Figure 7) identified numerous *Rpi-blb* homologues derived from different *Solanum* species. Alignment of these additional sequences with those presented in Figure 10 will help identify *Rpi-blb* homologues and specific amino-acid residues therein responsible for *P. infestans* resistance specificity. Furthermore, testing additional sequences in the above described phylogenetic tree analyses, e.g. using the Neighbour-Joining method of Saitou and Nei (1987), provides additional identification of genes belonging to the *Rpi-blb* gene cluster.

Artificial variants

[0064] Domain swaps between the different homologues can be made to ascertain the role of the different sequences in *P. infestans* resistance. The restriction enzyme *NsiI* for example, which recognises the DNA sequence ATGCAT present in the conserved MHD motif can be used to swap the complete LRR domain of *Rpi-blb* with that of *RGC1-blb* or *RGC3-blb* using techniques known to those skilled in the art. Chimeric variants of the *Rpi-blb* gene were made which encode the N-terminal half of Rpi-blb and the C-terminal half of RGC1-blb or RGC3-blb and visa versa, i.e., the N-terminal half of RGC1-blb or RGC3-blb and the C-terminal half of Rpi-blb (Figure 11). These variants were transformed to the susceptible potato genotype Impala and tested for *P. infestans* resistance. Chimeric *RGC3-blb* genes containing the LRR domain of *Rpi-blb* were resistant to *P. infestans* indicating that the specificity of the *Rpi-blb* gene is encoded by this part of the gene.

Table 1.

Overview of *P. Infestans* susceptibility in different *S. bulbocastanum* accessions							
S. bulbocastanum accession			#	#	#	%	
CGN	BGRC	PI	plants	R	V	susceptibi lity	cluster[a]
17692	8005	275193	11	10	1	9	a
	8006	275194	16	15	1	6	a
17693	8008	275198	19	18		0	b
17687	7997	243505	35	25	4	14	b
17688	7999	255518	19	19	0	0	c

a The letters a, b and c represent relative geographical origins depicted in Figure 1

Table 2. Overview of markers used for mapping *Rpi-blb*

Marker	Ori[a]	Sequence[b]	Annealing temp (°C)	Restriction enzyme[c]
TG513	F	CGTAAACGCACCAAAAGCAG	58	a.s.
	R	GATTCAAGCCAGGAACCGAG		
TG330	F	CAGCTGCCACAGCTCAAGC	56	TaqI
	R	TACCTACATGTACAGTACTGC		
CT88	F	GGCAGAAGAGCTAGGAAGAG	57	MboI
	R	ATGGCGTGATACAATCCGAG		
	F	TTCAAGAGCTTGAAGACATAACA	60	a.s.
	R	ATGGCGTGATACAATCCGAG		
CT64	F	ACTAGAGGATAGATTCTTGG	56	CfoI
	R	CTGGATGCCTTTCTCTATGT		
B139R	F	GATCAGAAGTGCCTTGAACC	56	TaqI
	R	CAAGGAGCTTGGTCAGCAG		
SPB33L	F	ATTGCACAGGAGCAGATCTG	59	HinfI
	R	TGTAAGAGAGCAAGAGGCAC		
SPB42L	F	AGAGCAGTCTTGAAGGTTGG	58	CfoI
	R	GATGGTAACTAAGCCTCAGG		
B149R	F	GACAGATTTCTCATAAACCTGC	58	MseI / XbaI
	R	AATCGTGCATCACTAGAGCG		
RGC1-4	F	TGTGGAGTAAGAGAGGAAGG	62	SspI / MseI
	R	TCAGCTGAGCAGTGTGTGG		
A	F	ATGGCTGAAGCTTTCATTCAAGTTCTG	60	
	R	TCACACCGCTTGATCAGTTGTGGAC		
B	F	TRCATGAYCTMATCCATGATTTGC	60	
	R	GMAATTTTGTGCCAGTCTTCTCC		

[a] Orientation of the primer, F: forward, R: reverse

[b] primer sequences according to IUB codes

[c] a.s.: allele specific.

Table 3.

Phytophthora infestans resistance assays		
Genotype[a]	RGC-containing plants/ transformants	R plants / RGC-containing plants
R0(RGC1-blb)	15/20[b]	0/15
R0(RGC2-blb)	7/31[c]	6/7
Ro(RGC3-blb)	0/6[c]	-
	14/21[d]	0/14
R0(RGC4-blb)	1/7[c]	0/1
	18/19[b]	0/18

[a] R0 genotypes are primary transformants obtained from transformation of the susceptible potato cultivar Impala with a T-DNA constructs containing the Rpi-blb gene candidates RGC1-blb, RGC2-blb, RGC3-blb or RGC4-blb. Agrobacteriumtumefaciens strains AGLO[b], LBA4404[c], or UIA143[d] were used for transformation of the P. infestans susceptible potato cultivar Impala. Kan[R]: Kanamycin resistant.

Table 4

Comparison of nucleotide and amino acid sequence homology								Rice RGC	Arabidops is RGC	Tomato I2C-1
			8005-8 BAC SPB4							
		RGC3- blb		RGC1-blb		RGC4-blb				
Rpi- blb	nt a	88		84		81		-	-	-
	aa a	81		76		70		37	32	32
		N[b]	Cb	N	C	N	C			
		91	71	79	72	75	66			

[a] Percentage nucleotide (nt) and amino acid (aa) sequence identity.
[b] Separate comparisons were made for the N-terminal (N) and C-terminal (C) halves of the protein sequences. The border between the two halves is the conserved Nsil restriction site in the DNA sequence (position 1417 of the Rpi-blb coding sequence).

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[0065]

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Rpi-blb protein sequence domain A, B and C

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Arg Leu Ser Ser Met Phe Ser Thr Ile Gln Ala Val Leu Glu Asp Ala
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Thr Lys Ala Thr Arg Phe Ser Gln Ser Glu Tyr Gly Arg Tyr His Pro
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Lys Val Ile Pro Phe Arg His Lys Val Gly Lys Arg Met Asp Gln Val
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His Glu Lys Ile Val Glu Arg Gln Ala Val Arg Arg Glu Thr Gly Ser
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Val Leu Thr Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu
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Gln Met Val Phe Asn Asp Gln Arg Val Thr Glu His Phe His Ser Lys
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Ile Trp Ile Cys Val Ser Glu Asp Phe Asp Glu Lys Arg Leu Ile Lys
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Ala Ile Val Glu Ser Ile Glu Gly Arg Pro Leu Leu Gly Glu Met Asp
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Tyr Leu Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Gln Lys Trp
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Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu
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Gln Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu
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Phe Met Gln Arg Ala Phe Gly His Gln Glu Ile Asn Pro Asn Leu
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Val Ala Ile Gly Lys Glu Ile Val Lys Lys Ser Gly Gly Val Pro Leu
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34

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Arg Val Lys Asn Asp Lys Asp Ala Lys Glu Ala Asn Leu Ser Ala Lys
            660             665             670

Gly Asn Leu His Ser Leu Ser Met Ser Trp Asn Asn Phe Gly Pro His
        675             680             685

Ile Tyr Glu Ser Glu Glu Val Lys Val Leu Glu Ala Leu Lys Pro His
    690             695             700

Ser Asn Leu Thr Ser Leu Lys Ile Tyr Gly Phe Arg Gly Ile His Leu
705             710             715             720

Pro Glu Trp Met Asn His Ser Val Leu Lys Asn Ile Val Ser Ile Leu
            725             730             735

Ile Ser Asn Phe Arg Asn Cys Ser Cys Leu Pro Pro Phe Gly Asp Leu
```

```
                    740                    745                    750
        Pro Cys Leu Glu Ser Leu Glu Leu His Trp Gly Ser Ala Asp Val Glu
                755                     760                 765
        Tyr Val Glu Glu Val Asp Ile Asp Val His Ser Gly Phe Pro Thr Arg
                770                     775                 780
        Ile Arg Phe Pro Ser Leu Arg Lys Leu Asp Ile Trp Asp Phe Gly Ser
        785                     790                 795                 800
        Leu Lys Gly Leu Leu Lys Lys Glu Gly Glu Gln Phe Pro Val Leu
                        805                 810                 815
        Glu Glu Met Ile Ile His Glu Cys Pro Phe Leu Thr Leu Ser Ser Asn
                        820                 825                 830
        Leu Arg Ala Leu Thr Ser Leu Arg Ile Cys Tyr Asn Lys Val Ala Thr
                    835                 840                 845
        Ser Phe Pro Glu Glu Met Phe Lys Asn Leu Ala Asn Leu Lys Tyr Leu
                850                 855                 860
        Thr Ile Ser Arg Cys Asn Asn Leu Lys Glu Leu Pro Thr Ser Leu Ala
        865                 870                 875                 880
        Ser Leu Asn Ala Leu Lys Ser Leu Lys Ile Gln Leu Cys Cys Ala Leu
                    885                 890                 895
        Glu Ser Leu Pro Glu Glu Gly Leu Glu Gly Leu Ser Ser Leu Thr Glu
                900                 905                 910
        Leu Phe Val Glu His Cys Asn Met Leu Lys Cys Leu Pro Glu Gly Leu
                915                 920                 925
        Gln His Leu Thr Thr Leu Thr Ser Leu Lys Ile Arg Gly Cys Pro Gln
            930                 935                 940
        Leu Ile Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp His Lys Ile
        945                 950                 955                 960
        Ser His Ile Pro Asn Val Asn Ile Tyr Ile
                        965                 970
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<210> 42
<211> 979
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: alignment
      RGC3-blb

<220>
<221> SITE
<222> (1)..(979)

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<400> 42
Met Ala Glu Ala Phe Ile Gln Val Val Leu Asp Asn Leu Thr Ser Phe
1               5                   10                  15
Leu Lys Gly Glu Leu Val Leu Leu Phe Gly Phe Gln Asp Glu Phe Gln
                20                  25                  30
Arg Leu Ser Ser Met Phe Ser Thr Ile Gln Ala Val Leu Glu Asp Ala
            35                  40                  45
```

```
         Gln Glu Lys Gln Leu Asn Asp Lys Pro Leu Glu Asn Trp Leu Gln Lys
             50              55              60

 5       Leu Asn Ala Ala Thr Tyr Glu Val Asp Asp Ile Leu Asp Glu Tyr Lys
         65              70              75              80

         Thr Lys Ala Thr Arg Phe Leu Gln Ser Glu Tyr Gly Arg Tyr His Pro
                     85              90              95

10       Lys Val Ile Pro Phe Arg His Lys Val Gly Lys Arg Met Asp Gln Val
                     100             105             110

         Met Lys Lys Leu Asn Ala Ile Ala Glu Glu Arg Lys Asn Phe His Leu
                 115             120             125

15       Gln Glu Lys Ile Ile Glu Arg Gln Ala Ala Thr Arg Glu Thr Gly Ser
                 130             135             140

         Val Leu Thr Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu
         145             150             155             160

20       Ile Val Lys Ile Leu Ile Asn Asn Val Ser Asp Ala Gln Lys Leu Ser
                     165             170             175

         Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ser
                     180             185             190

25       Gln Met Val Phe Asn Asp Gln Arg Val Thr Glu Arg Phe Tyr Pro Lys
                 195             200             205

         Ile Trp Ile Cys Val Ser Asp Asp Phe Asp Glu Lys Arg Leu Ile Lys
             210             215             220

30       Ala Ile Val Glu Ser Ile Glu Gly Lys Ser Leu Ser Asp Met Asp Leu
         225             230             235             240

         Ala Pro Leu Gln Lys Lys Leu Gln Glu Leu Leu Asn Gly Lys Arg Tyr
                     245             250             255

35       Phe Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln His Lys Trp Ala
                     260             265             270

         Asn Leu Arg Ala Val Leu Lys Val Gly Ala Ser Gly Ala Phe Val Leu
                 275             280             285

40       Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu Gln
         290             295             300

         Pro Tyr Glu Leu Ser Asn Leu Ser Pro Glu Asp Cys Trp Phe Leu Phe
         305             310             315             320

45       Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn Pro Asn Leu Val
                 325             330             335

         Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala
                 340             345             350

50       Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Glu Glu Arg Glu
                 355             360             365

         Trp Glu His Val Arg Asp Ser Pro Ile Trp Asn Leu Pro Gln Asp Glu
             370             375             380

         Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro Leu
55       385             390             395             400

         Asp Leu Asp Gln Cys Phe Val Tyr Cys Ala Val Phe Pro Lys Asp Thr
                     405             410             415
```

37

Lys Met Ala Lys Glu Asn Leu Ile Ala Phe Trp Met Ala His Gly Phe
420   425   430

Leu Leu Ser Lys Gly Asn Leu Glu Leu Glu Asp Val Gly Asn Glu Val
435   440   445

Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val Glu
450   455   460

Ser Gly Lys Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu Ala
465   470   475   480

Thr Ser Leu Phe Ser Ala Asn Thr Ser Ser Ser Asn Ile Arg Glu Ile
485   490   495

Asn Ala Asn Tyr Asp Gly Tyr Met Met Ser Ile Gly Phe Ala Glu Val
500   505   510

Val Ser Ser Tyr Ser Pro Ser Leu Leu Gln Lys Phe Val Ser Leu Arg
515   520   525

Val Leu Asn Leu Arg Asn Ser Asn Leu Asn Gln Leu Pro Ser Ser Ile
530   535   540

Gly Asp Leu Val His Leu Arg Tyr Leu Asp Leu Ser Gly Asn Phe Arg
545   550   555   560

Ile Arg Asn Leu Pro Lys Arg Leu Cys Lys Leu Gln Asn Leu Gln Thr
565   570   575

Leu Asp Leu His Tyr Cys Asp Ser Leu Ser Cys Leu Pro Lys Gln Thr
580   585   590

Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Gly Cys Ser Leu
595   600   605

Thr Ser Thr Pro Pro Arg Ile Gly Leu Leu Thr Cys Leu Lys Ser Leu
610   615   620

Ser Cys Phe Val Ile Gly Lys Arg Lys Gly Tyr Gln Leu Gly Glu Leu
625   630   635   640

Lys Asn Leu Asn Leu Tyr Gly Ser Ile Ser Ile Thr Lys Leu Asp Arg
645   650   655

Val Lys Lys Asp Ser Asp Ala Lys Glu Ala Asn Leu Ser Ala Lys Ala
660   665   670

Asn Leu His Ser Leu Cys Leu Ser Trp Asp Leu Asp Gly Lys His Arg
675   680   685

Tyr Asp Ser Glu Val Leu Glu Ala Leu Lys Pro His Ser Asn Leu Lys
690   695   700

Tyr Leu Glu Ile Asn Gly Phe Gly Gly Ile Arg Leu Pro Asp Trp Met
705   710   715   720

Asn Gln Ser Val Leu Lys Asn Val Val Ser Ile Arg Ile Arg Gly Cys
725   730   735

Glu Asn Cys Ser Cys Leu Pro Pro Phe Gly Glu Leu Pro Cys Leu Glu
740   745   750

Ser Leu Glu Leu His Thr Gly Ser Ala Asp Val Glu Tyr Val Glu Asp
755   760   765

Asn Val His Pro Gly Arg Phe Pro Ser Leu Arg Lys Leu Val Ile Trp

```
              770                 775                 780
      Asp Phe Ser Asn Leu Lys Gly Leu Leu Lys Lys Glu Gly Glu Glu Gln
      785                 790                 795                 800

      Phe Pro Val Leu Glu Glu Met Thr Phe Tyr Trp Cys Pro Met Phe Val
                      805                 810                 815

      Ile Pro Thr Leu Ser Ser Val Lys Thr Leu Lys Val Ile Ala Thr Asp
                      820                 825                 830

      Ala Thr Val Leu Arg Ser Ile Ser Asn Leu Arg Ala Leu Thr Ser Leu
                  835                 840                 845

      Asp Ile Ser Asn Asn Val Glu Ala Thr Ser Leu Pro Glu Glu Met Phe
          850                 855                 860

      Lys Ser Leu Ala Asn Leu Lys Tyr Leu Asn Ile Ser Phe Phe Arg Asn
      865                 870                 875                 880

      Leu Lys Glu Leu Pro Thr Ser Leu Ala Ser Leu Asn Ala Leu Lys Ser
                      885                 890                 895

      Leu Lys Phe Glu Phe Cys Asn Ala Leu Glu Ser Leu Pro Ala Glu Gly
                  900                 905                 910

      Val Lys Gly Leu Thr Ser Leu Thr Glu Leu Ser Val Ser Asn Cys Met
                  915                 920                 925

      Met Leu Lys Cys Leu Pro Glu Gly Leu Gln His Leu Thr Ala Leu Thr
          930                 935                 940

      Thr Leu Thr Ile Thr Gln Cys Pro Ile Val Phe Lys Arg Cys Glu Arg
      945                 950                 955                 960

      Gly Ile Gly Glu Asp Trp His Lys Ile Ala His Ile Pro Tyr Leu Thr
                      965                 970                 975

      Leu Tyr Glu
```

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<210> 43
<211> 992
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: alignment
      RGC1-blb

<220>
<221> SITE
<222> (1)..(992)

<400> 43
Met Ala Glu Ala Phe Leu Gln Val Leu Leu Asp Asn Leu Thr Phe Phe
1               5                   10                  15

Ile Gln Gly Glu Leu Gly Leu Val Phe Gly Phe Glu Lys Glu Phe Lys
                20                  25                  30

Lys Leu Ser Ser Met Phe Ser Met Ile Gln Ala Val Leu Glu Asp Ala
            35                  40                  45

Gln Glu Lys Gln Leu Lys Tyr Lys Ala Ile Lys Asn Trp Leu Gln Lys
            50                  55                  60
```

Leu Asn Val Ala Ala Tyr Glu Val Asp Asp Ile Leu Asp Asp Cys Lys
65   70   75   80

Thr Glu Ala Ala Arg Phe Lys Gln Ala Val Leu Gly Arg Tyr His Pro
                    85   90   95

Arg Thr Ile Thr Phe Cys Tyr Lys Val Gly Lys Arg Met Lys Glu Met
                100   105   110

Met Glu Lys Leu Asp Ala Ile Ala Glu Glu Arg Arg Asn Phe His Leu
            115   120   125

Asp Glu Arg Ile Ile Glu Arg Gln Ala Ala Arg Arg Gln Thr Gly Phe
        130   135   140

Val Leu Thr Glu Pro Lys Val Tyr Gly Arg Glu Lys Glu Glu Asp Glu
145   150   155   160

Ile Val Lys Ile Leu Ile Asn Asn Val Ser Tyr Ser Glu Glu Val Pro
                165   170   175

Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ala
                180   185   190

Gln Met Val Phe Asn Asp Gln Arg Ile Thr Glu His Phe Asn Leu Lys
            195   200   205

Ile Trp Val Cys Val Ser Asp Asp Phe Asp Glu Lys Arg Leu Ile Lys
        210   215   220

Ala Ile Val Glu Ser Ile Glu Gly Lys Ser Leu Gly Asp Met Asp Leu
225   230   235   240

Ala Pro Leu Gln Lys Lys Leu Gln Glu Leu Leu Asn Gly Lys Arg Tyr
                245   250   255

Phe Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Glu Lys Trp Asp
            260   265   270

Asn Leu Arg Ala Val Leu Lys Ile Gly Ala Ser Gly Ala Ser Ile Leu
        275   280   285

Ile Thr Thr Arg Leu Glu Lys Ile Gly Ser Ile Met Gly Thr Leu Gln
    290   295   300

Leu Tyr Gln Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu Phe
305   310   315   320

Lys Gln Arg Ala Phe Cys His Gln Thr Glu Thr Ser Pro Lys Leu Met
                325   330   335

Glu Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala
            340   345   350

Ala Lys Thr Leu Gly Gly Leu Leu Arg Phe Lys Arg Glu Glu Ser Glu
        355   360   365

Trp Glu His Val Arg Asp Ser Glu Ile Trp Asn Leu Pro Gln Asp Glu
    370   375   380

Asn Ser Val Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro Leu
385   390   395   400

Asp Leu Arg Gln Cys Phe Ala Tyr Cys Ala Val Phe Pro Lys Asp Thr
            405   410   415

Lys Ile Glu Lys Glu Tyr Leu Ile Ala Leu Trp Met Ala His Ser Phe
            420   425   430

40

Leu Leu Ser Lys Gly Asn Met Glu Leu Glu Asp Val Gly Asn Glu Val
435   440   445

Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val Lys
450   455   460

Ser Gly Lys Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu Ala
465   470   475   480

Thr Ser Met Phe Ser Ala Ser Ala Ser Ser Arg Ser Ile Arg Gln Ile
485   490   495

Asn Val Lys Asp Asp Glu Asp Met Met Phe Ile Val Thr Asn Tyr Lys
500   505   510

Asp Met Met Ser Ile Gly Phe Ser Glu Val Val Ser Ser Tyr Ser Pro
515   520   525

Ser Leu Phe Lys Arg Phe Val Ser Leu Arg Val Leu Asn Leu Ser Asn
530   535   540

Ser Glu Phe Glu Gln Leu Pro Ser Ser Val Gly Asp Leu Val His Leu
545   550   555   560

Arg Tyr Leu Asp Leu Ser Gly Asn Lys Ile Cys Ser Leu Pro Lys Arg
565   570   575

Leu Cys Lys Leu Gln Asn Leu Gln Thr Leu Asp Leu Tyr Asn Cys Gln
580   585   590

Ser Leu Ser Cys Leu Pro Lys Gln Thr Ser Lys Leu Cys Ser Leu Arg
595   600   605

Asn Leu Val Leu Asp His Cys Pro Leu Thr Ser Met Pro Pro Arg Ile
610   615   620

Gly Leu Leu Thr Cys Leu Lys Thr Leu Gly Tyr Phe Val Val Gly Glu
625   630   635   640

Arg Lys Gly Tyr Gln Leu Gly Glu Leu Arg Asn Leu Asn Leu Arg Gly
645   650   655

Ala Ile Ser Ile Thr His Leu Glu Arg Val Lys Asn Asp Met Glu Ala
660   665   670

Lys Glu Ala Asn Leu Ser Ala Lys Ala Asn Leu His Ser Leu Ser Met
675   680   685

Ser Trp Asp Arg Pro Asn Arg Tyr Glu Ser Glu Glu Val Lys Val Leu
690   695   700

Glu Ala Leu Lys Pro His Pro Asn Leu Lys Tyr Leu Glu Ile Ile Asp
705   710   715   720

Phe Cys Gly Phe Cys Leu Pro Asp Trp Met Asn His Ser Val Leu Lys
725   730   735

Asn Val Val Ser Ile Leu Ile Ser Gly Cys Glu Asn Cys Ser Cys Leu
740   745   750

Pro Pro Phe Gly Glu Leu Pro Cys Leu Glu Ser Leu Glu Leu Gln Asp
755   760   765

Gly Ser Val Glu Val Glu Tyr Val Glu Asp Ser Gly Phe Leu Thr Arg
770   775   780

Arg Arg Phe Pro Ser Leu Arg Lys Leu His Ile Gly Gly Phe Cys Asn

```
            785                 790                 795                 800
        Leu Lys Gly Leu Gln Arg Met Lys Gly Ala Glu Gln Phe Pro Val Leu
                        805                 810                 815

        Glu Glu Met Lys Ile Ser Asp Cys Pro Met Phe Val Phe Pro Thr Leu
                    820                 825                 830

        Ser Ser Val Lys Lys Leu Glu Ile Trp Gly Glu Ala Asp Ala Gly Gly
                    835                 840                 845

        Leu Ser Ser Ile Ser Asn Leu Ser Thr Leu Thr Ser Leu Lys Ile Phe
                850                 855                 860

        Ser Asn His Thr Val Thr Ser Leu Leu Glu Glu Met Phe Lys Asn Leu
        865                 870                 875                 880

        Glu Asn Leu Ile Tyr Leu Ser Val Ser Phe Leu Glu Asn Leu Lys Glu
                        885                 890                 895

        Leu Pro Thr Ser Leu Ala Ser Leu Asn Asn Leu Lys Cys Leu Asp Ile
                    900                 905                 910

        Arg Tyr Cys Tyr Ala Leu Glu Ser Leu Pro Glu Glu Gly Leu Glu Gly
                915                 920                 925

        Leu Ser Ser Leu Thr Glu Leu Phe Val Glu His Cys Asn Met Leu Lys
                930                 935                 940

        Cys Leu Pro Glu Gly Leu Gln His Leu Thr Thr Leu Thr Ser Leu Lys
        945                 950                 955                 960

        Ile Arg Gly Cys Pro Gln Leu Ile Lys Arg Cys Glu Lys Gly Ile Gly
                        965                 970                 975

        Glu Asp Trp His Lys Ile Ser His Ile Pro Asn Val Asn Ile Tyr Ile
                    980                 985                 990
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<210> 44
<211> 1040
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: alignment
     RGC4-b1b

<220>
<221> SITE
<222> (1)..(1040)

<400> 44
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        Met Ala Glu Ala Phe Leu Gln Val Leu Leu Glu Asn Leu Thr Ser Phe
        1                   5                   10                  15

        Ile Gly Asp Lys Leu Val Leu Ile Phe Gly Phe Glu Lys Glu Cys Glu
                    20                  25                  30

        Lys Leu Ser Ser Val Phe Ser Thr Ile Gln Ala Val Leu Gln Asp Ala
                    35                  40                  45

        Gln Glu Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
                50                  55                  60

        Leu Asn Ser Ala Ala Tyr Glu Val Asp Asp Ile Leu Gly Glu Cys Lys
        65                  70                  75                  80
```

```
      Asn Glu Ala Ile Arg Phe Glu Gln Ser Arg Leu Gly Phe Tyr His Pro
                      85                  90                      95

      Gly Ile Ile Asn Phe Arg His Lys Ile Gly Arg Arg Met Lys Glu Ile
                     100             105             110

      Met Glu Lys Leu Asp Ala Ile Ser Glu Glu Arg Arg Lys Phe His Phe
                 115             120             125

      Leu Glu Lys Ile Thr Glu Arg Gln Ala Ala Ala Thr Arg Glu Thr
         130             135             140

      Val Gly Trp Gln Trp Gly Trp Ala Arg Leu Glu Tyr Lys Arg Leu Leu
      145             150             155             160

      Leu Gly Val Leu Met Arg Ile Met Ser Leu Arg Met His Val Ser Thr
                     165             170             175

      Cys Ser Thr Leu Tyr Glu Phe Lys Phe Tyr Leu Cys Thr Pro Lys Val
                 180             185             190

      Gly Ala Arg Arg Cys Phe Val Leu Thr Glu Pro Lys Val Tyr Gly Arg
                 195             200             205

      Asp Lys Glu Glu Asp Glu Ile Val Lys Ile Leu Ile Asn Asn Val Asn
         210             215             220

      Val Ala Glu Glu Leu Pro Val Phe Pro Ile Ile Gly Met Gly Gly Leu
      225             230             235             240

      Gly Lys Thr Thr Leu Ala Gln Met Ile Phe Asn Asp Glu Arg Val Thr
                     245             250             255

      Lys His Phe Asn Pro Lys Ile Trp Val Cys Val Ser Asp Asp Phe Asp
                 260             265             270

      Glu Lys Arg Leu Ile Lys Thr Ile Ile Gly Asn Ile Glu Arg Ser Ser
                 275             280             285

      Pro His Val Glu Asp Leu Ala Ser Phe Gln Lys Lys Leu Gln Glu Leu
         290             295             300

      Leu Asn Gly Lys Arg Tyr Leu Leu Val Leu Asp Asp Val Trp Asn Asp
      305             310             315             320

      Asp Leu Glu Lys Trp Ala Lys Leu Arg Ala Val Leu Thr Val Gly Ala
                     325             330             335

      Arg Gly Ala Ser Ile Leu Ala Thr Thr Arg Leu Glu Lys Val Gly Ser
                     340             345             350

      Ile Met Gly Thr Leu Gln Pro Tyr His Leu Ser Asn Leu Ser Pro His
                 355             360             365

      Asp Ser Leu Leu Leu Phe Met Gln Arg Ala Phe Gly Gln Gln Lys Glu
         370             375             380

      Ala Asn Pro Asn Leu Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys
      385             390             395             400

      Gly Gly Val Pro Leu Ala Ala Lys Thr Leu Gly Gly Leu Leu Arg Phe
                     405             410             415

      Lys Arg Glu Glu Ser Glu Trp Glu His Val Arg Asp Asn Glu Ile Trp
                 420             425             430

      Ser Leu Pro Gln Asp Glu Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser
                 435             440             445
```

```
Tyr His His Leu Pro Leu Asp Leu Arg Gln Cys Phe Ala Tyr Cys Ala
    450             455             460
Val Phe Pro Lys Asp Thr Lys Met Ile Lys Glu Asn Leu Ile Thr Leu
465             470             475             480
Trp Met Ala His Gly Phe Leu Leu Ser Lys Gly Asn Leu Glu Leu Glu
            485             490             495
Asp Val Gly Asn Glu Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe
            500             505             510
Gln Glu Ile Glu Ala Lys Ser Gly Asn Thr Tyr Phe Lys Ile His Asp
        515             520             525
Leu Ile His Asp Leu Ala Thr Ser Leu Phe Ser Ala Ser Ala Ser Cys
    530             535             540
Gly Asn Ile Arg Glu Ile Asn Val Lys Asp Tyr Lys His Thr Val Ser
545             550             555             560
Ile Gly Phe Ala Ala Val Val Ser Ser Tyr Ser Pro Ser Leu Leu Lys
            565             570             575
Lys Phe Val Ser Leu Arg Val Leu Asn Leu Ser Tyr Ser Lys Leu Glu
            580             585             590
Gln Leu Pro Ser Ser Ile Gly Asp Leu Leu His Leu Arg Tyr Leu Asp
        595             600             605
Leu Ser Cys Asn Asn Phe Arg Ser Leu Pro Glu Arg Leu Cys Lys Leu
    610             615             620
Gln Asn Leu Gln Thr Leu Asp Val His Asn Cys Tyr Ser Leu Asn Cys
625             630             635             640
Leu Pro Lys Gln Thr Ser Lys Leu Ser Ser Leu Arg His Leu Val Val
            645             650             655
Asp Gly Cys Pro Leu Thr Ser Thr Pro Pro Arg Ile Gly Leu Leu Thr
            660             665             670
Cys Leu Lys Thr Leu Gly Phe Phe Ile Val Gly Ser Lys Lys Gly Tyr
        675             680             685
Gln Leu Gly Glu Leu Lys Asn Leu Asn Leu Cys Gly Ser Ile Ser Ile
    690             695             700
Thr His Leu Glu Arg Val Lys Asn Asp Thr Asp Ala Glu Ala Asn Leu
705             710             715             720
Ser Ala Lys Ala Asn Leu Gln Ser Leu Ser Met Ser Trp Asp Asn Asp
            725             730             735
Gly Pro Asn Arg Tyr Glu Ser Lys Glu Val Lys Val Leu Glu Ala Leu
            740             745             750
Lys Pro His Pro Asn Leu Lys Tyr Leu Glu Ile Ile Ala Phe Gly Gly
        755             760             765
Phe Arg Phe Pro Ser Trp Ile Asn His Ser Val Leu Glu Lys Val Ile
    770             775             780
Ser Val Arg Ile Lys Ser Cys Lys Asn Cys Leu Cys Leu Pro Pro Phe
785             790             795             800
Gly Glu Leu Pro Cys Leu Glu Asn Leu Glu Leu Gln Asn Gly Ser Ala
```

44

```
                    805                    810                    815
Glu Val Glu Tyr Val Glu Glu Asp Asp Val His Ser Arg Phe Ser Thr
            820                 825                 830

Arg Arg Ser Phe Pro Ser Leu Lys Lys Leu Arg Ile Trp Phe Phe Arg
            835             840             845

Ser Leu Lys Gly Leu Met Lys Glu Glu Gly Glu Glu Lys Phe Pro Met
    850             855                 860

Leu Glu Glu Met Ala Ile Leu Tyr Cys Pro Leu Phe Val Phe Pro Thr
865             870             875                     880

Leu Ser Ser Val Lys Lys Leu Glu Val His Gly Asn Thr Asn Thr Arg
            885             890                     895

Gly Leu Ser Ser Ile Ser Asn Leu Ser Thr Leu Thr Ser Leu Arg Ile
        900             905                 910

Gly Ala Asn Tyr Arg Ala Thr Ser Leu Pro Glu Glu Met Phe Thr Ser
        915             920             925

Leu Thr Asn Leu Glu Phe Leu Ser Phe Phe Asp Phe Lys Asn Leu Lys
    930             935             940

Asp Leu Pro Thr Ser Leu Thr Ser Leu Asn Ala Leu Lys Arg Leu Gln
945             950             955                     960

Ile Glu Ser Cys Asp Ser Leu Glu Ser Phe Pro Glu Gln Gly Leu Glu
            965                 970                 975

Gly Leu Thr Ser Leu Thr Gln Leu Phe Val Lys Tyr Cys Lys Met Leu
            980                 985             990

Lys Cys Leu Pro Glu Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu
        995                 1000            1005

Gly Val Ser Gly Cys Pro Glu Val Glu Lys Arg Cys Asp Lys Glu Ile
    1010            1015                1020

Gly Glu Asp Trp His Lys Ile Ala His Ile Pro Asn Leu Asp Ile His
1025            1030            1035                1040
```

Claims

1. An isolated or recombinant nucleic acid or functional fragment thereof corresponding to one of a cluster of genes identifiable by phylogenetic tree analyses as corresponding to the *Rpi-blb, RGC1-blb, RGC3-blb and RGC4-blb* cluster of figure 9.

2. A nucleic acid according to claim 1 said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* family with resistance against an oomycete pathogen, or a functional equivalent thereof.

3. A nucleic acid according to claim 1 or 2 wherein said member of the *Solanacae* family comprises *S. tuberosum.*

4. A nucleic acid according to claim 1 to 3 where said resistance is race non-specific.

5. A nucleic acid according to claim 1 to 4 comprising a sequence as depicted in figure 6 for Rpi-blb or part thereof.

6. A nucleic acid according to claim 1 to 5 at least comprising a LRR domain.

7. A vector comprising a nucleic acid according to anyone of claims 1 to 6.

8. A host cell comprising a nucleic acid according to anyone of claims 1 to 6 or a vector according to claim 7.

9. A cell according to claim 8 comprising a plant cell.

10. A cell according to claim 9 wherein said plant comprises a member of the *Solanacae* family.

11. A plant comprising a cell according to anyone of claims 6 to 10.

12. A part derived from a plant according to claim 11.

13. A part according to claim 12 wherein said tuber comprises a potato or said fruit comprises a tomato.

14. Progeny of a plant according to claim 11.

15. A proteinaceous substance exhibiting the characteristic of providing at least partial resistance to an oomycete infection such as caused by a *Phytophthora* species when incorporated and expressed in a plant or plant cell.

16. A proteinaceous substance encoded by a nucleic acid according to anyone of claims 1 to 6.

17. A proteinaceous substance comprising an amino acid sequence as depicted in figure 8 or part thereof.

18. A binding molecule directed at a substance according to anyone of claims 15 to 17.

19. A binding molecule according to claim 18 comprising an antibody or fragment thereof.

20. A binding molecule directed at a nucleic acid according to anyone of claim 1 to 6.

21. A binding molecule according to claim 20 comprising a probe or primer.

22. A binding molecule according to anyone of claims 18 to 21 provided with a label.

23. A binding molecule according to claim 22 wherein said label comprises an excitable moiety.

24. Use of a nucleic acid according to anyone of claims 1 to 6 or a vector according to claim 7 or a cell according to anyone of claims 8 to 11 or a substance according to anyone of claims 15 to 17 or a binding molecule according to anyone of claims 18 to 23 in a method for providing a plant or its progeny with resistance against an oomycete infection.

25. Use according to claim 24 wherein said oomycete comprises *Phytophthora infestans.*

26. Use according to claim 24 or 25 wherein said plant comprises S. *tuberosum.*

27. A method for providing a plant or its progeny with at least partial resistance against an oomycete infection comprising providing said plant or part thereof with a gene or functional fragment thereof comprising a nucleic acid corresponding to one of a cluster of genes identifiable by phylogenetic tree analyses as corresponding to the *Rpi-blb, RCG1-blb, RCG3-blb* and *RCG4-blb*cluster of figure 9, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* with resistance against an oomycete fungus, or providing said plant or part thereof with a nucleic acid according to anyone of claims 1 to 4 or a vector according to claim 5 or a cell according to claim 6 or a substance according to anyone of claims 15 to 18.

28. A method for selecting a plant or plant material or progeny thereof for its susceptibility or resistance to an oomycete infection comprising testing at least part of said plant or plant material or progeny thereof for the presence or absence of a nucleic acid corresponding to one of a cluster of genes identifiable by phylogenetic tree analyses as corresponding to the *Rpi-blb, RCG1-blb, RCG3-blb* and *RCG4-blb*cluster of figure 9, said nucleic acid encoding a gene product that is capable of providing a member of the *Solanacae* with resistance against an oomycete fungus.

29. A method according to claim 28 comprising contacting at least part of said plant or plant material or progeny thereof with a binding molecule according to anyone of claims 19 to 23 and determining the binding of said molecule to said part.

30. A method according to claim 29 wherein said oomycete comprises *Phytophthora infestans*.

31. A method according to claim 28 or 29 wherein said plant comprises *S. tuberosum*.

32. An isolated *S. bulbocastanum*, or part thereof, susceptible to an oomycete infection caused by *Phytophthora infestans*.
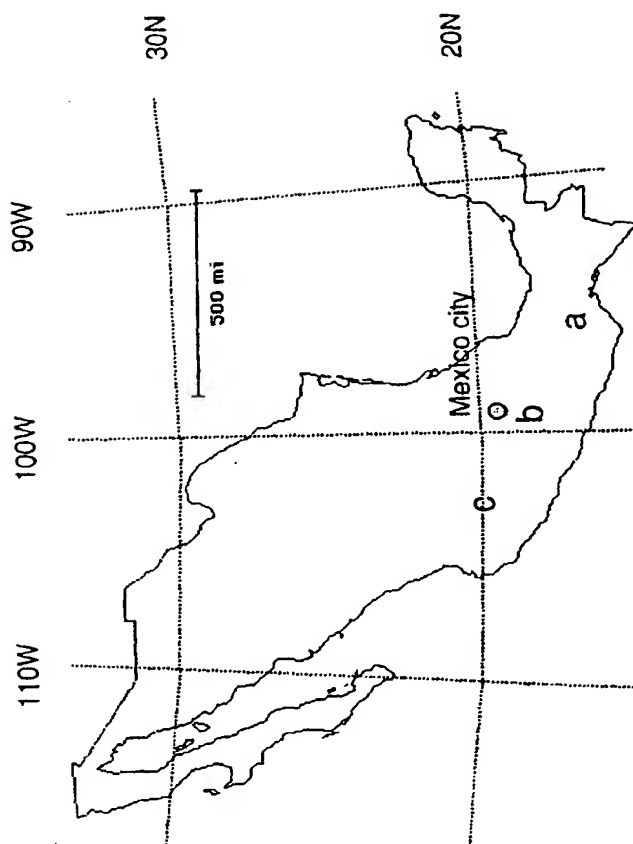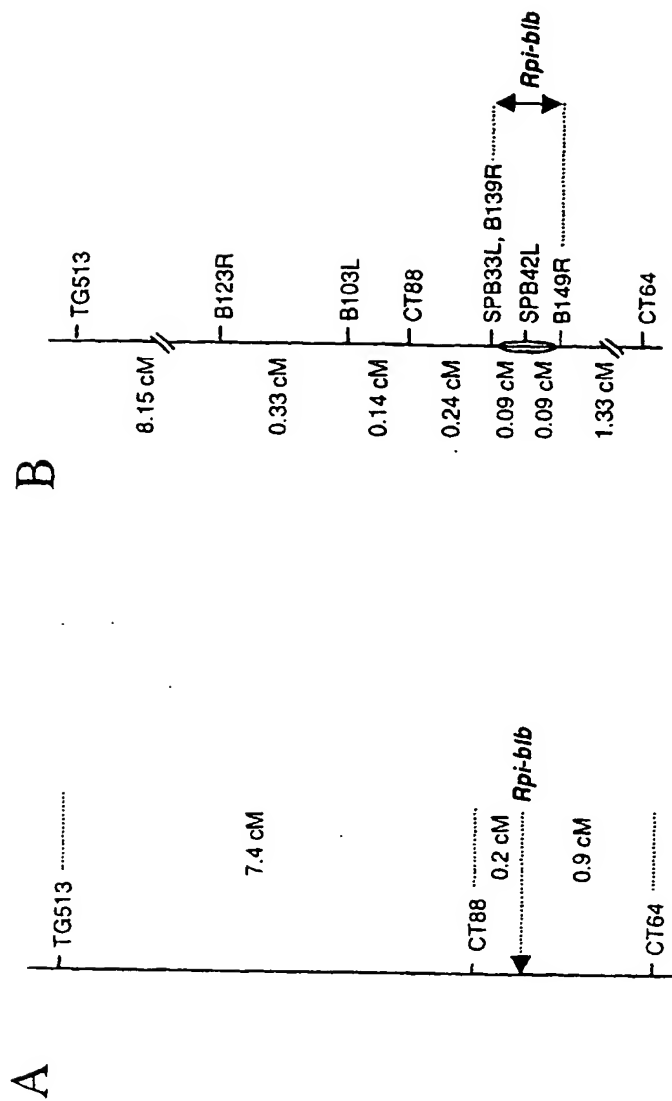
Figure 1
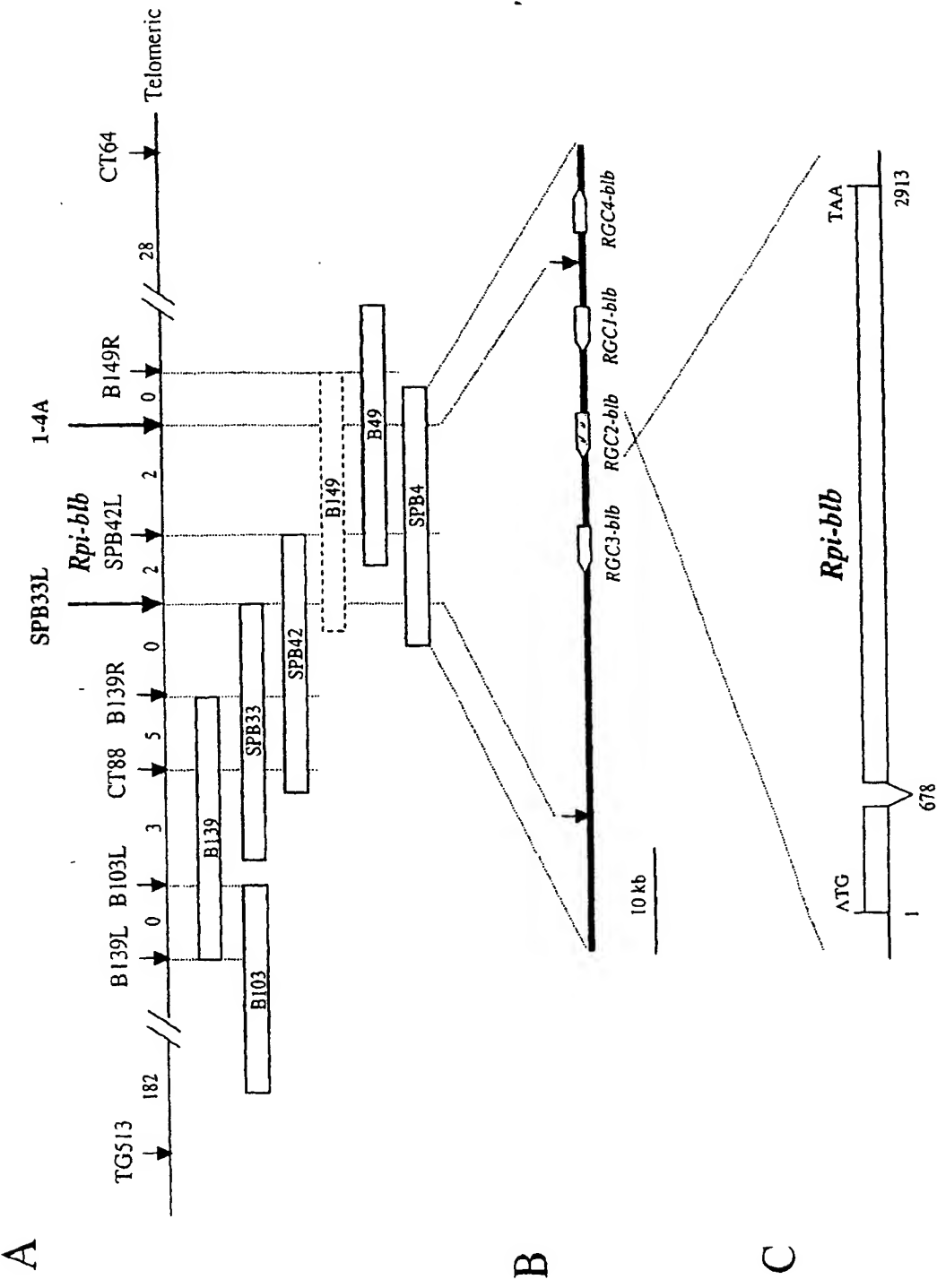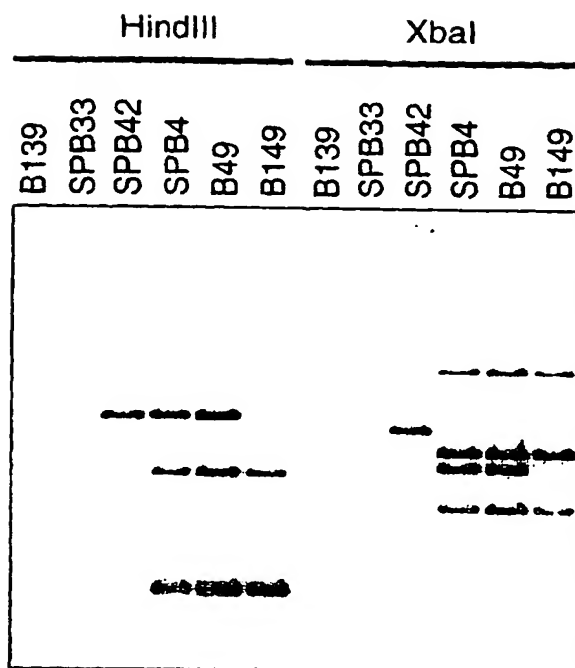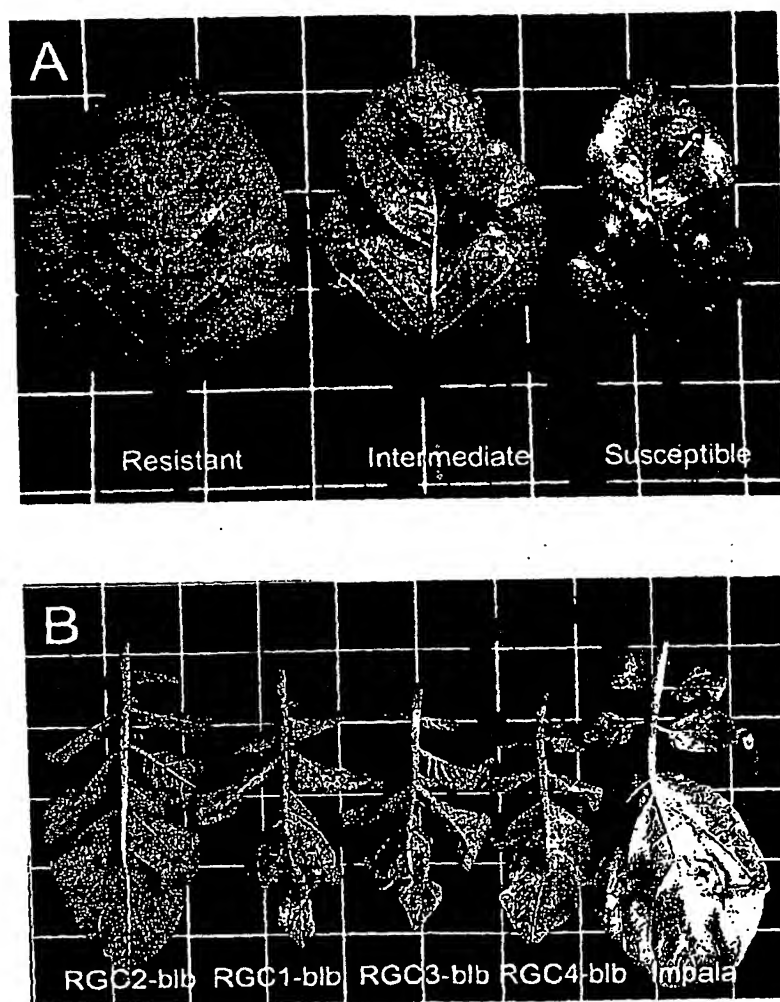
Figure 2

Figure 3

Figure 4

Figure 5

Figure 6A

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   1    ATGGCTGAAGCTTTCATTCAAGTTCTGCTAGACAATCTCACTTCTTTCCT

  51    CAAAGGGGAACTTGTATTGCTTTTCGGTTTTCAAGATGAGTTCCAAAGGC

 101    TTTCAAGCATGTTTTCTACAATTCAAGCCGTCCTTGAAGATGCTCAGGAG

 151    AAGCAACTCAACAACAAGCCTCTAGAAAATTGGTTGCAAAAACTCAATGC

 201    TGCTACATATGAAGTCGATGACATCTTGGATGAATATAAAACCAAGGCCA

 251    CAAGATTCTCCCAGTCTGAATATGGCCGTTATCATCCAAAGGTTATCCCT

 301    TTCCGTCACAAGGTCGGGAAAAGGATGGACCAAGTGATGAAAAAACTAAA

 351    GGCAATTGCTGAGGAAAGAAAGAATTTTCATTTGCACGAAAAAATTGTAG

 401    AGAGACAAGCTGTTAGACGGGAAACAGGTTCTGTATTAACCGAACCGCAG

 451    GTTTATGGAAGAGACAAAGAGAAGATGAGATAGTGAAAATCCTAATAAA

 501    CAATGTTAGTGATGCCCAACACCTTTCAGTCCTCCCAATACTTGGTATGG

 551    GGGGATTAGGAAAAACGACTCTTGCCCAAATGGTCTTCAATGACCAGAGA

 601    GTTACTGAGCATTTCCATTCCAAAATATGGATTTGTGTCTCGGAAGATTT

 651    TGATGAGAAGAGGTTAATAAAGGCAATTGTAGAATCTATTGAAGGAAGGC

 701    CACTACTTGGTGAGATGGACTTGGCTCCACTTCAAAAGAAGCTTCAGGAG

 751    TTGCTGAATGGAAAAGATACTTGCTTGTCTTAGATGATGTTTGGAATGA

 801    AGATCAACAGAAGTGGGCTAATTTAAGAGCAGTCTTGAAGGTTGGAGCAA

 851    GTGGTGCTTCTGTTCTAACCACTACTCGTCTTGAAAAGGTTGGATCAATT

 901    ATGGGAACATTGCAACCATATGAACTGTCAAATCTGTCTCAAGAAGATTG

 951    TTGGTTGTTGTTCATGCAACGTGCATTTGGACACCAAGAAGAAATAAATC

1001    CAAACCTTGTGGCAATCGGAAAGGAGATTGTGAAAAAAGTGGTGGTGTG
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1101   AAGAGCATGGGAACATGTGAGAGACAGTCCGATTTGGAATTTGCCTCAAG

1151   ATGAAAGTTCTATTCTGCCTGCCCTGAGGCTTAGTTACCATCAACTTCCA

1201   CTTGATTTGAAACAATGCTTTGCGTATTGTGCGGTGTTCCCAAAGGATGC

1251   CAAAATGGAAAAAGAAAGCTAATCTCTCTGGATGGCGCATGGTTTTC

1301   TTTTATCAAAAGGAAACATGGAGCTAGAGGATGTGGGCGATGAAGTATGG

1351   AAAGAATTATACTTGAGGTCTTTTTTCCAAGAGATTGAAGTTAAAGATGG

1401   TAAAACTTATTTCAAGATGCATGATCTCATCCATGATTTGGCAACATCTC

1451   TGTTTTCAGCAAACACATCAAGCAGCAATATCCGTGAAATAAATAAACAC

1501   AGTTACACACATATGATGTCCATTGGTTTCGCCGAAGTGGTGTTTTTTTA

1551   CACTCTTCCCCCCTTGGAAAAGTTTATCTCGTTAAGAGTGCTTAATCTAG

1601   GTGATTCGACATTTAATAAGTTACCATCTTCCATTGGAGATCTAGTACAT

1651   TTAAGATACTTGAACCTGTATGGCAGTGGCATGCGTAGTCTTCCAAAGCA

1701   GTTATGCAAGCTTCAAAATCTGCAAACTCTTGATCTACAATATTGCACCA

1751   AGCTTTGTTGTTTGCCAAAAGAAACAAGTAAACTTGGTAGTCTCCGAAAT

1801   CTTTTACTTGATGGTAGCCAGTCATTGACTTGTATGCCACCAAGGATAGG

1851   ATCATTGACATGCCTTAAGACTCTAGGTCAATTTGTTGTTGGAAGGAAGA

1901   AAGGTTATCAACTTGGTGAACTAGGAAACCTAAATCTCTATGGCTCAATT

1951   AAAATCTCGCATCTTGAGAGAGTGAAGAATGATAAGGACGCAAAAGAAGC

2001   CAATTTATCTGCAAAAGGGAATCTGCATTCTTTAAGCATGAGTTGGAATA

2051   ACTTTGGACCACATATATATGAATCAGAAGAAGTTAAAGTGCTTGAAGCC

2101   CTCAAACCACACTCCAATCTGACTTCTTTAAAAATCTATGGCTTCAGAGG

2151   AATCCATCTCCCAGAGTGGATGAATCACTCAGTATTGAAAAATATTGTCT

2201   CTATTCTAATTAGCAACTTCAGAAACTGCTCATGCTTACCACCCTTTGGT

2251   GATCTGCCTTGTCTAGAAAGTCTAGAGTTACACTGGGGGTCTGCGGATGT

2301   GGAGTATGTTGAAGAAGTGGATATTGATGTTCATTCTGGATTCCCCACAA

2351   GAATAAGGTTTCCATCCTTGAGGAAACTTGATATATGGGACTTTGGTAGT

2401   CTGAAAGGATTGCTGAAAAAGGAAGGAGAAGAGCAATTCCCTGTGCTTGA

2451   AGAGATGATAATTCACGAGTGCCCTTTTCTGACCCTTTCTTCTAATCTTA

2501   GGGCTCTTACTTCCCTCAGAATTTGCTATAATAAAGTAGCTACTTCATTC

2551   CCAGAAGAGATGTTCAAAAACCTTGCAAATCTCAAATACTTGACAATCTC

2601   TCGGTGCAATAATCTCAAAGAGCTGCCTACCAGCTTGGCTAGTCTGAATG

2651   CTTTGAAAAGTCTAAAAATTCAATTGTGTTGCGCACTAGAGAGTCTCCCT

2701   GAGGAAGGGCTGGAAGGTTTATCTTCACTCACAGAGTTATTTGTTGAACA

2751   CTGTAACATGCTAAAATGTTTACCAGAGGGATTGCAGCACCTAACAACCC

2801   TCACAAGTTTAAAAATTCGGGGATGTCCACAACTGATCAAGCGGTGTGAG

2851   AAGGGAATAGGAGAAGACTGGCACAAAATTTCTCACATTCCTAATGTGAA

2901   TATATATATTTAA

Figure 6B

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1      ATGGCTGAAGCTTTCATTCAAGTTCTGCTAGACAATCTCACTTCTTTCCT
51     CAAAGGGGAACTTGTATTGCTTTTCGGTTTTCAAGATGAGTTCCAAAGGC
101    TTTCAAGCATGTTTTCTACAATTCAAGCCGTCCTTGAAGATGCTCAGGAG
151    AAGCAACTCAACAACAAGCCTCTAGAAAATTGGTTGCAAAAACTCAATGC
201    TGCTACATATGAAGTCGATGACATCTTGGATGAATATAAAACCAAGGCCA
251    CAAGATTCTCCCAGTCTGAATATGGCCGTTATCATCCAAAGGTTATCCCT
301    TTCCGTCACAAGGTCGGGAAAAGGATGGACCAAGTGATGAAAAAACTAAA
351    GGCAATTGCTGAGGAAAGAAAGAATTTTCATTTGCACGAAAAAATTGTAG
401    AGAGACAAGCTGTTAGACGGGAAACAGGTACTCATCTTAAATTAGTATTA
451    CAACAACTAAGTTTATATTCATTTTTTTGGCAATTATCAAATTCAGAAAA
501    GGGTTAAATATACTCATGTCCTATCGTAAATAGTGTATATATACCTCTCG
551    TTGTACTTTCGATCTGAATATACTTGTCAAATCTGGCAAGCTCAGAATCA
601    AATTATCCACCCCAACTTTTAAATACTCGATATCTTTAGAAATCCACCTG
651    TCTAACTCATCCACTACCCATTCCCTTTGCTTTGAATTCTTTTCTTTACC
701    TATAAACTTGGAACACTCGATCCGTTTTGCTTTTCTTAACAAAGCAGCTC
751    AGAGAAAAGAGGTTTTCTTCTATTCTGTTTCTCTGTGTGCTGCACTTGGG
801    TCCTTAATCCCATTAAAAACAGGGCATGTTAATCCCAACGACGGTAGCCT
851    TTCCTGACAGCTGACTGTAAATTTTGTCTAACAAAGAAAAAAAAAGATTA
901    GACATGTTTTTCCTTGTCATTGATTAGGCTGGATTTCTTTCAGAGTGGAA
951    CATAGGGGATATATTGGACCAAAAGTAGAATGGGTATATATTTAAAGTAT
1001   TTCTGATAGAACAGGAGTATATTGTGCGAAAATATCCTCTATTTTCTGTT
1051   GTCTCCTAATGAGTTTGAATGTAATAATATTCTCATGTGGACATTGCTTG
1101   CACCAGGTTCTGTATTAACCGAACCGCAGGTTTATGGAAGAGACAAAGAG
1151   AAAGATGAGATAGTGAAAATCCTAATAAACAATGTTAGTGATGCCCAACA
1201   CCTTTCAGTCCTCCCAATACTTGGTATGGGGGGATTAGGAAAAACGACTC
1251   TTGCCCAAATGGTCTTCAATGACCAGAGAGTTACTGAGCATTTCCATTCC
1301   AAAATATGGATTTGTGTCTCGGAAGATTTTGATGAGAAGAGGTTAATAAA
1351   GGCAATTGTAGAATCTATTGAAGGAAGGCCACTACTTGGTGAGATGGACT
1401   TGGCTCCACTTCAAAAGAAGCTTCAGGAGTTGCTGAATGGAAAAAGATAC
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1451   TTGCTTGTCTTAGATGATGTTTGGAATGAAGATCAACAGAAGTGGGCTAA

1501   TTTAAGAGCAGTCTTGAAGGTTGGAGCAAGTGGTGCTTCTGTTCTAACCA

1551   CTACTCGTCTTGAAAAGGTTGGATCAATTATGGGAACATTGCAACCATAT

1601   GAACTGTCAAATCTGTCTCAAGAAGATTGTTGGTTGTTGTTCATGCAACG

1651·  TGCATTTGGACACCAAGAAGAAATAAATCCAAACCTTGTGGCAATCGGAA

1701   AGGAGATTGTGAAAAAAGTGGTGGTGTGCCTCTAGCAGCCAAAACTCTT

1751   GGAGGTATTTTGTGCTTCAAGAGAGAAGAAAGAGCATGGGAACATGTGAG

1801   AGACAGTCCGATTTGGAATTTGCCTCAAGATGAAAGTTCTATTCTGCCTG

1851   CCCTGAGGCTTAGTTACCATCAACTTCCACTTGATTTGAAACAATGCTTT

1901   GCGTATTGTGCGGTGTTCCCAAAGGATGCCAAAATGGAAAAGAAAAGCT

1951   AATCTCTCTGGATGGCGCATGGTTTTCTTTTATCAAAAGGAAACATGG

2001   AGCTAGAGGATGTGGGCGATGAAGTATGGAAAGAATTATACTTGAGGTCT

2051   TTTTTCCAAGAGATTGAAGTTAAAGATGGTAAAACTTATTTCAAGATGCA

2101   TGATCTCATCCATGATTTGGCAACATCTCTGTTTTCAGCAAACACATCAA

2151   GCAGCAATATCCGTGAAATAAATAAACACAGTTACACACATATGATGTCC

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2251   GTTTATCTCGTTAAGAGTGCTTAATCTAGGTGATTCGACATTTAATAAGT

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2351   GGCAGTGGCATGCGTAGTCTTCCAAAGCAGTTATGCAAGCTTCAAAATCT

2401   GCAAACTCTTGATCTACAATATTGCACCAAGCTTTGTTGTTTGCCAAAAG

2451   AAACAAGTAAACTTGGTAGTCTCCGAAATCTTTTACTTGATGGTAGCCAG

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2551   TCTAGGTCAATTTGTTGTTGGAAGGAAGAAAGGTTATCAACTTGGTGAAC

2601   TAGGAAACCTAAATCTCTATGGCTCAATTAAAATCTCGCATCTTGAGAGA

2651   GTGAAGAATGATAAGGACGCAAAAGAAGCCAATTTATCTGCAAAAGGGAA

2701   TCTGCATTCTTTAAGCATGAGTTGGAATAACTTTGGACCACATATATATG

2751   AATCAGAAGAAGTTAAAGTGCTTGAAGCCCTCAAACCACACTCCAATCTG

2801   ACTTCTTTAAAAATCTATGGCTTCAGAGGAATCCATCTCCCAGAGTGGAT

2851   GAATCACTCAGTATTGAAAAATATTGTCTCTATTCTAATTAGCAACTTCA

2901   GAAACTGCTCATGCTTACCACCCTTTGGTGATCTGCCTTGTCTAGAAAGT

2951   CTAGAGTTACACTGGGGGTCTGCGGATGTGGAGTATGTTGAAGAAGTGGA

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3051    GGAAACTTGATATATGGGACTTTGGTAGTCTGAAAGGATTGCTGAAAAAG
3101    GAAGGAGAAGAGCAATTCCCTGTGCTTGAAGAGATGATAATTCACGAGTG
3151    CCCTTTTCTGACCCTTTCTTCTAATCTTAGGGCTCTTACTTCCCTCAGAA
3201    TTTGCTATAATAAAGTAGCTACTTCATTCCCAGAAGAGATGTTCAAAAAC
3251    CTTGCAAATCTCAAATACTTGACAATCTCTCGGTGCAATAATCTCAAAGA
3301    GCTGCCTACCAGCTTGGCTAGTCTGAATGCTTTGAAAAGTCTAAAAATTC
3351    AATTGTGTTGCGCACTAGAGAGTCTCCCTGAGGAAGGGCTGGAAGGTTTA
3401    TCTTCACTCACAGAGTTATTTGTTGAACACTGTAACATGCTAAAATGTTT
3451    ACCAGAGGGATTGCAGCACCTAACAACCCTCACAAGTTTAAAAATTCGGG
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Figure 6C

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201   TTGGCGAACAATAATGTTGTTGATTATCACTTTCTGAATAAATGTTGTGT
251   CACTTGGAAAAAACACCAAATAGAACTATTCATGTTTTTTCTTTAGTATA
301   TATAAATATGATCTTTAACTTAATTGCAGCAGACAGGCATGATCTTTAAC
351   TTTAAATGTGCACAAGTAGATTGACAGGCTTGCTAATTGAGTGTCTGTTA
401   TAATCAGTATTAATTACTCTCAAGGTAATAGTATATTCCAGACAAATTTT
451   GTGTTACCAAATTAAATATATTTCTAAAACTCTCCTCAAAGTAGTTAATA
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551   TGAAATTTACTTTCTAGTTAAATTGGTCAAAGTTGAAAGAATTTCAAGTG
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901   TCCTTTCATACTAATGATAAATTTTTTTTTTTTTTTTTTTTTTTACTAAT
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1401  CAAAAATTCAATTAATATGAAATGGAGAGAGTAACTTTATTTTAGAGGCA
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1601  TACATTGCAATTTTTTGCATATCAATATGATAAAAAAATATATCGTAAAA
1651  TATTAGTCAAAATTTTTATAATTTGACTCAAATCATGAAAGTATAATAA
1701  TTAATAGTGGACGGAGGAAGTATTGTCTTTCCAGATTTGTGGCCATTTTT
1751  GGTCCAAGGGCCATTAGCAGTTCTCTTCATTTTCTACTTCTGTCTCATAT
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2101  TTCTAACCATTCACTACACTATATTATGCATTTTATCCGCCAATGACTTA
2151  TTTCAGCTTTAATTAATTAGGAAAGAGGAAACTGCCAATGAGGAAGAGTA
2201  GGGGCGTAGTTGCTGTCGACGAAAAAAAGATAATACTCACTCTTTTCGAT
2251  TTTTATTTTTATTTATCACTTTTAACCTATCATGTAAAAGATAATTATT
2301  TTTTTCATGCTTTATCCTTAGTATTAAACAATTTAATAGGGATTATTTTG
2351  TAAAATATTTATATGAATAATTGTTTTCGTAATGAATTTGTCCGGTCAAA
2401  CAATGATAAATAAAAATGAATGAAGAGAGTAGAAAACAAAACAAAAGAAC
2451  AAGTTGACAACTTGAGAGATTAAAAGGGTCCAAAACGCCTTGGATTTTGA
2501  GATTCCATATGTGAAATTTCCATGAAATAATTGAATTTGTATTATTACAA
2551  GTCAAACTTTCCATTTCATTCCAACTAGCCATCTTGGTTTCAAAATTACA
2601  CATTCATTCATTCACAGATCTAATATTCTTAATAGTGATTTCCACAT ATG
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3151    TTAAATATACTCATGTCCTATCGTAAATAGTGTATATATACCTCTCGTTG
3201    TACTTTCGATCTGAATATACTTGTCAAATCTGGCAAGCTCAGAATCAAAT
3251    TATCCACCCCAACTTTTAAATACTCGATATCTTTAGAAATCCACCTGTCT
3301    AACTCATCCACTACCCATTCCCTTTGCTTTGAATTCTTTTCTTTACCTAT
3351    AAACTTGGAACACTCGATCCGTTTTGCTTTTCTTAACAAAGCAGCTCAGA
3401    GAAAAGAGGTTTTCTTCTATTCTGTTTCTCTGTGTGCTGCACTTGGGTCC
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3551    ATGTTTTTCCTTGTCATTGATTAGGCTGGATTTCTTTCAGAGTGGAACAT
3601    AGGGGATATATTGGACCAAAAGTAGAATGGGTATATATTTAAAGTATTTC
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3701    TCCTAATGAGTTTGAATGTAATAATATTCTCATGTGGACATTGCTTGCAC
3751    CAGGTTCTGTATTAACCGAACCGCAGGTTTATGGAAGAGACAAAGAGAAA
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3851    TTCAGTCCTCCCAATACTTGGTATGGGGGGATTAGGAAAAACGACTCTTG
3901    CCCAAATGGTCTTCAATGACCAGAGAGTTACTGAGCATTTCCATTCCAAA
3951    ATATGGATTTGTGTCTCGGAAGATTTTGATGAGAAGAGGTTAATAAAGGC
4001    AATTGTAGAATCTATTGAAGGAAGGCCACTACTTGGTGAGATGGACTTGG
4051    CTCCACTTCAAAAGAAGCTTCAGGAGTTGCTGAATGGAAAAAGATACTTG
4101    CTTGTCTTAGATGATGTTTGGAATGAAGATCAACAGAAGTGGGCTAATTT
4151    AAGAGCAGTCTTGAAGGTTGGAGCAAGTGGTGCTTCTGTTCTAACCACTA
4201    CTCGTCTTGAAAAGGTTGGATCAATTATGGGAACATTGCAACCATATGAA
4251    CTGTCAAATCTGTCTCAAGAAGATTGTTGGTTGTTGTTCATGCAACGTGC
4301    ATTTGGACACCAAGAAGAAATAAATCCAAACCTTGTGGCAATCGGAAAGG
4351    AGATTGTGAAAAAAGTGGTGGTGTGCCTCTAGCAGCCAAAACTCTTGGA
4401    GGTATTTTGTGCTTCAAGAGAGAAGAAAGAGCATGGGAACATGTGAGAGA
4451    CAGTCCGATTTGGAATTTGCCTCAAGATGAAAGTTCTATTCTGCCTGCCC
4501    TGAGGCTTAGTTACCATCAACTTCCACTTGATTTGAAACAATGCTTTGCG
4551    TATTGTGCGGTGTTCCCAAAGGATGCCAAAATGGAAAAGAAAAGCTAAT
4601    CTCTCTCTGGATGGCGCATGGTTTTCTTTTATCAAAAGGAAACATGGAGC
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4651   TAGAGGATGTGGGCGATGAAGTATGGAAAGAATTATACTTGAGGTCTTTT
4701   TTCCAAGAGATTGAAGTTAAAGATGGTAAAACTTATTTCAAGATGCATGA
4751   TCTCATCCATGATTTGGCAACATCTCTGTTTTCAGCAAACACATCAAGCA
4801   GCAATATCCGTGAAATAAATAAACACAGTTACACACATATGATGTCCATT
4851·  GGTTTCGCCGAAGTGGTGTTTTTTTACACTCTTCCCCCCTTGGAAAAGTT
4901   TATCTCGTTAAGAGTGCTTAATCTAGGTGATTCGACATTTAATAAGTTAC
4951   CATCTTCCATTGGAGATCTAGTACATTTAAGATACTTGAACCTGTATGGC
5001   AGTGGCATGCGTAGTCTTCCAAAGCAGTTATGCAAGCTTCAAAATCTGCA
5051   AACTCTTGATCTACAATATTGCACCAAGCTTTGTTGTTTGCCAAAAGAAA
5101   CAAGTAAACTTGGTAGTCTCCGAAATCTTTTACTTGATGGTAGCCAGTCA
5151   TTGACTTGTATGCCACCAAGGATAGGATCATTGACATGCCTTAAGACTCT
5201   AGGTCAATTTGTTGTTGGAAGGAAGAAAGGTTATCAACTTGGTGAACTAG
5251   GAAACCTAAATCTCTATGGCTCAATTAAAATCTCGCATCTTGAGAGAGTG
5301   AAGAATGATAAGGACGCAAAAGAAGCCAATTTATCTGCAAAAGGGAATCT
5351   GCATTCTTTAAGCATGAGTTGGAATAACTTTGGACCACATATATATGAAT
5401   CAGAAGAAGTTAAAGTGCTTGAAGCCCTCAAACCACACTCCAATCTGACT
5451   TCTTTAAAAATCTATGGCTTCAGAGGAATCCATCTCCCAGAGTGGATGAA
5501·  TCACTCAGTATTGAAAAATATTGTCTCTATTCTAATTAGCAACTTCAGAA
5551   ACTGCTCATGCTTACCACCCTTTGGTGATCTGCCTTGTCTAGAAAGTCTA
5601   GAGTTACACTGGGGGTCTGCGGATGTGGAGTATGTTGAAGAAGTGGATAT
5651   TGATGTTCATTCTGGATTCCCCACAAGAATAAGGTTTCCATCCTTGAGGA
5701   AACTTGATATATGGGACTTTGGTAGTCTGAAAGGATTGCTGAAAAAGGAA
5751   GGAGAAGAGCAATTCCCTGTGCTTGAAGAGATGATAATTCACGAGTGCCC
5801   TTTTCTGACCCTTTCTTCTAATCTTAGGGCTCTTACTTCCCTCAGAATTT
5851   GCTATAATAAAGTAGCTACTTCATTCCCAGAAGAGATGTTCAAAAACCTT
5901   GCAAATCTCAAATACTTGACAATCTCTCGGTGCAATAATCTCAAAGAGCT
5951   GCCTACCAGCTTGGCTAGTCTGAATGCTTTGAAAAGTCTAAAAATTCAAT
6001   TGTGTTGCGCACTAGAGAGTCTCCCTGAGGAAGGGCTGGAAGGTTTATCT
6051   TCACTCACAGAGTTATTTGTTGAACACTGTAACATGCTAAAATGTTTACC
6101   AGAGGGATTGCAGCACCTAACAACCCTCACAAGTTTAAAAATTCGGGGAT
6151   GTCCACAACTGATCAAGCGGTGTGAGAAGGGAATAGGAGAAGACTGGCAC
6201   AAAATTTCTCACATTCCTAATGTGAATATATATATTTAAGTTATTTGCTA
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6251   TTGTTTCTTTGTTTGTGAGTCTTTTTGGTTCCTGCCATTGTGATTGCATG
6301   TAATTTTTTTCTAGGGTTGTTTGTTTGTTGAGTCTCTCTCTCATTGGATG
6351   TAATTCTCTTTTGGTAACAAATTAACAATCTATTTGTATTATACGCTTTC
6401   AGAATCTATTACTTATTTGTAATTGTTTCTTTGTTTGTAAATTGTGAGTA
6451   TCTTATTGTATGGAATTTTCTGATTTTATTTTGAAAACAAATCAATAAGA
6501   TCCATCTGTATTATACTCCCTTCGTCTCATTTTATGTGACACTTTTTGGA
6551   TTTCGAGATTCTTTGATCTTAAATTTTTCATAGATCTTTTAAACATTTTG
6601   AATTATCAATTATTGAGATTTTAGTATTTTTTATGTAGTTTACAAATATA
6651   TAAAATTAATTTTTTAAAAAAAAGAAGATTTCATGCGCATATTCCCGATC
6701   AAACTTAAATTACTAGACTCTCGAAAAATGAAAGTGTCACATAAATTGA
6751   GACAGAGGGAGTACTTGTTAATGTTGTAATTATTGGCGAACAATAATGTT
6801   GGTGATTATCACTTTCTGAATAAATGTTGTGTCACGTGGAAAAAACACCA
6851   AATAGAAGTATTCATGCTTTTTTAGTATATATAAACATGATTTTTAACTT
6901   GGTTTCAGCGGATAGTCATGACCTTTAACTCTGAATGTGCACAAGTAGAT
6951   ACTTGTATAAAATTAAACAAATTTTATAAAATTATACAATATGACACTGA
7001   GAGTAATTGATACCAATTGCAGTCGTTGCTGCTTTTCGATTCTCTGTCAT
7051   TCTCTAGGTAATTGATTTTACAGAAAAGGGCCAAAAATATCCCTGAAGTA
7101   CCAGAAAAGGTCTCAAAATACCAACCATCCACATTTTGGTCTAAAAATAT
7151   CCTTCTACTCATCCTTTTTTGTCTAAAATTACCCTTTCATCCACATTTTT
7201   GCTCACTTATACCCTTATAACAACTCTCTCCTTTTTTAAAAAAAAAATATT
7251   TATTATGTGTCATTTTCTTATTGAATGAAATAAAAATCCACCTCTATTAA
7301   TTTTTTCCCATAATTTATCCAAATCAAAACAATATATTTTTTCAAGATC
```

Figure 6D

```
   1   ATGGCTGAAGCTTTCCTTCAAGTTCTGCTAGATAATCTCACTTTTTTCAT
  51   CCAAGGGGAACTTGGATTGGTTTTTGGTTTCGAGAAGGAGTTTAAAAAAC
 101   TTTCAAGTATGTTTTCAATGATCCAAGCTGTGCTAGAAGATGCTCAAGAG
 151   AAGCAACTGAAGTACAAGGCAATAAAGAACTGGTTACAGAAACTCAATGT
 201   TGCTGCATATGAAGTTGATGACATCTTGGATGACTGTAAAACTGAGGCAG
 251   CAAGATTCAAGCAGGCTGTATTGGGGCGTTATCATCCACGGACCATCACT
 301   TTCTGTTACAAGGTGGGAAAAAGAATGAAAGAAATGATGGAAAAACTAGA
 351   TGCAATTGCAGAGGAACGGAGGAATTTTCATTTAGATGAAAGGATTATAG
 401   AGAGACAAGCTGCTAGACGGCAAACAGGTGCTCATCTTAATTTTATTTTA
 451   AAACAAATAAGTATTACAAATTGCAGAGAAACGAAGGAATTTATATTCAT
 501   TTTTATTTTTGGCAATTATCAAAGTCATTTGTGTTTTTAAGCTGGGGGGA
 551   AGTTTCAAATATTTTCTCTAGTCTTAATGTTTGTCTCACTCACTCAGCAT
 601   GATTTTCTCAATCCTTCACTTCAACTCCCCCCTACTGTGCAAATATCTTC
 651   TCTATTTTCTGTTGACTCCTAATGAGCTTGAATGTAACAACATTCTTGTT
 701   TGGAGCAGGTTTTGTTTTAACTGAGCCAAAAGTTTATGGAAGGGAAAAAG
 751   AGGAGGATGAGATAGTGAAAATCTTGATAAACAATGTTAGTTATTCCGAA
 801   GAAGTTCCAGTACTCCCAATACTTGGTATGGGGGGACTAGGAAAGACGAC
 851   TCTAGCCCAAATGGTCTTCAATGATCAAAGAATTACTGAGCATTTCAATC
 901   TAAAGATATGGGTTTGTGTCTCAGATGATTTTGATGAGAAGAGGTTGATT
 951   AAGGCAATTGTAGAATCTATTGAAGGAAAGTCACTGGGTGACATGGACTT
1001   GGCTCCCCTCCAGAAAAAGCTTCAGGAGTTGTTGAATGGAAAAAGATACT
1051   TTCTTGTTTTGGATGATGTTTGGAATGAAGATCAAGAAAAGTGGGATAAT
1101   CTTAGAGCAGTATTGAAGATTGGAGCTAGTGGTGCTTCAATTCTAATTAC
1151   TACTCGTCTTGAAAAAATTGGATCAATTATGGGAACTTTGCAACTATATC
1201   AGTTATCAAATTTGTCTCAAGAAGATTGTTGGTTGTTGTTCAAGCAACGT
1251   GCATTTTGCCACCAAACCGAAACAAGTCCTAAACTTATGGAAATCGGAAA
1301   GGAGATTGTGAAGAAATGTGGGGGTGTGCCTCTAGCAGCCAAAACTCTTG
1351   GAGGCCTTTTACGCTTCAAGAGGGAAGAAAGTGAATGGGAACATGTGAGA
1401   GATAGTGAGATTTGGAATTTACCTCAAGATGAAAATTCTGTTTTGCCTGC
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1451   CCTGAGGCTGAGTTATCATCATCTTCCACTTGATTTGAGACAATGTTTTG
1501   CATATTGCGCAGTATTCCCAAAGGACACCAAAATAGAAAAGGAATATCTC
1551   ATCGCTCTCTGGATGGCACACAGTTTTCTTTTATCAAAAGGAAACATGGA
1601   GCTAGAGGATGTGGGCAATGAAGTATGGAATGAATTATACTTGAGGTCTT
1651   TTTTCCAAGAGATTGAAGTTAAATCTGGTAAAACTTATTTCAAGATGCAT
1701   GATCTCATCCATGATTTGGCTACATCTATGTTTTCAGCAAGCGCATCAAG
1751   CAGAAGTATACGCCAAATAAATGTAAAAGATGATGAAGATATGATGTTCA
1801   TTGTAACAAATTATAAAGATATGATGTCCATTGGTTTCTCCGAAGTGGTG
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1901   TAATCTAAGTAACTCAGAATTTGAACAGTTACCGTCTTCCGTTGGAGATC
1951   TAGTACATTTAAGATACCTTGACCTGTCTGGTAATAAAATTTGTAGTCTT
2001   CCAAAGAGGTTGTGCAAGCTTCAAAATCTGCAGACTCTTGATCTATATAA
2051   TTGCCAGTCACTTTCTTGTTTGCCGAAACAAACAAGTAAGCTTTGTAGTC
2101   TCCGGAATCTTGTACTTGATCACTGTCCATTGACTTCTATGCCACCAAGA
2151   ATAGGATTGTTGACATGCCTTAAGACACTAGGTTACTTTGTTGTAGGCGA
2201   GAGGAAAGGTTATCAACTTGGTGAACTACGAAATTTAAACCTCCGTGGTG
2251   CAATTTCAATCACACATCTTGAGAGAGTGAAAAATGATATGGAGGCAAAA
2301   GAAGCCAATTTATCTGCAAAAGCAAATCTACACTCTTTAAGCATGAGTTG
2351   GGATAGACCAAACAGATATGAATCCGAAGAAGTTAAAGTGCTTGAAGCCC
2401   TCAAACCACATCCCAATCTGAAATATTTAGAAATCATTGACTTCTGTGGA
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2501   TATTCTAATTAGCGGTTGTGAAAACTGCTCGTGCTTACCACCCTTTGGTG
2551   AGCTGCCTTGTCTAGAAAGTCTGGAGTTACAAGACGGGTCTGTGGAGGTG
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2651   GAGAAAACTTCATATAGGTGGCTTTTGTAATCTGAAAGGATTGCAGAGAA
2701   TGAAAGGAGCAGAGCAATTCCCCGTGCTTGAAGAGATGAAGATTTCGGAT
2751   TGCCCTATGTTTGTTTTTCCGACCCTTTCTTCTGTCAAGAAATTAGAAAT
2801   TTGGGGGGAGGCAGATGCAGGAGGTTTGAGCTCCATATCTAATCTCAGCA
2851   CTCTTACATCCCTCAAGATTTTCAGTAACCACACAGTGACTTCACTACTG
2901   GAAGAGATGTTCAAAAACCTTGAAAATCTCATATACTTGAGTGTCTCTTT
2951   CTTGGAGAATCTCAAAGAGCTGCCTACCAGCCTGGCTAGTCTCAACAATT
3001   TGAAGTGTCTGGATATTCGTTATTGTTACGCACTAGAGAGTCTCCCCGAG
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3101   TAACATGCTAAAATGTTTACCAGAGGGATTGCAGCACCTAACAACCCTCA

3151   CAAGTTTAAAAATTCGGGGATGTCCACAACTGATCAAGCGGTGTGAGAAG

3201   GGAATAGGAGAAGACTGGCACAAAATTTCTCACATTCCTAATGTGAATAT

3251   ATATATTTAA

Figure 6E

```
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101   TTTCAAGCATGTTTTCTACAATCCAAGCCGTCCTTGAAGATGCTCAAGAG
151   AAGCAACTCAACGACAAGCCTCTAGAAAATTGGTTGCAAAAACTCAATGC
201   TGCTACATATGAAGTCGATGACATCTTGGATGAATATAAAACTAAGGCCA
251   CAAGATTCTTGCAGTCTGAATATGGCCGTTATCATCCAAAGGTTATCCCT
301   TTCCGTCACAAGGTTGGGAAAAGGATGGACCAAGTGATGAAAAACTGAA
351   TGCAATTGCTGAGGAACGAAAGAATTTTCATTTGCAAGAAAGATTATAG
401   AGAGACAAGCTGCTACACGGGAAACAGGTACTCATCTTAAATTAGTATTA
451   CAACTTAGTTTATATTCATTTGTTTTGGGCAATGATCAAATTATGTAAAG
501   GTCAAATATACTCATGTACTACTGAAAATAGTTTAAATATACCTCTAGTT
551   ATACTATTAGTACGAACATACTCCTCCCATATACTTTGGAACAAATATTC
601   CCTTAACGAAATAAGACACGTGAAAAGTTCAGATTCAAATTATCCACCCT
651   CAATTTTAAGATCTGATTTCTTTAGGAAACCACTCATCTCCTCCGTTTTG
701   AGTTCTTAACGAAGCAGCTCAGAGAAAAGAGGTTTTCTTCTGTTCTGTTT
751   CTGCTGCATTTGTGTCTTAATCCAATAACAAACAATACAAATTAATATTA
801   TGTTCACGATGAGGGTAGTCTTTCTAGCTAGACATGAACTGAGTGTAAAT
851   TTTGTTTTAAGGAAGAAAAAGAAATGATTAGGCTGGATTTCTTTCAGAGT
901   GGAATATAGGGGGATAAAGTTGGAGCATAGAGTTCCATCGTTTATTTCTT
951   TCCTTAAAGTAACAAGTTCAACAAAATGATATCAAGGTACGGTAATGGAA
1001  AATTATTAGACACGTCTAAACTACAAAAATGGAATAGAAACTTAAATTAT
1051  CAGTGACAATATCATCCTTTAATAAAGCTACCAAATTTAAATCATGATAC
1101  AGAGAAGAAACCAAAAAAATTAGGGGTGAATTATTTGATTCTATGCTTAT
1151  CACATGTCTTCCCATCAACATCAAAGGAAAAATTGTGCCAAAGTATAAAC
1201  GGTGCGGTATATTTGGATTGAAAGTAAAACAGGAGGATACATTTGGACTA
1251  AAAGTATAACAATAAGTATATTTGATCATTTTATGTATCAAATTCATGTG
1301  GTTTTTGGGGAGAAGGGAAGTTTCAATGTTTTCAATCTGCTCCTCATCTC
1351  ATCCATATCTCTTTATTGTGCAAAACCCTTCTCTATTTAACTATTTTCTG
1401  CCGACTCCTAATGAGCTTGAATGTAACAATATTCTCATCTGGACATTGCT
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1551  AAACTCTCAGTCCTCCCAATACTTGGTATGGGGGGACTAGGAAAGACAAC
1601  TCTTTCCCAAATGGTCTTCAATGATCAGAGAGTAACTGAGCGTTTCTATC
1651  CCAAAATATGGATTTGCGTCTCGGATGATTTTGATGAGAAGAGGTTGATA
1701  AAGGCAATAGTAGAATCTATTGAAGGGAAGTCCCTCAGTGACATGGACTT
1751  GGCTCCACTTCAAAAGAAGCTTCAAGAGTTGCTGAATGGAAAAAGATACT
1801  TCCTTGTCTTAGATGATGTTTGGAATGAAGATCAACATAAGTGGGCTAAT
1851  TTAAGAGCAGTCTTGAAGGTTGGAGCAAGTGGTGCATTTGTTCTAACTAC
1901  TACTCGTCTTGAAAAGGTTGGATCAATTATGGGAACATTGCAACCATATG
1951  AATTGTCAAATCTGTCTCCAGAGGATTGTTGGTTTTTGTTCATGCAGCGT
2001  GCATTTGGACACCAAGAAGAAATAAATCCAAACCTTGTGGCAATCGGAAA
2051  GGAGATTGTGAAAAAATGTGGTGGTGTGCCTCTAGCAGCCAAGACTCTTG
2101  GAGGTATTTTGCGCTTCAAGAGAGAAGAAAGAGAATGGGAACATGTGAGA
2151  GACAGTCCGATTTGGAATTTGCCTCAAGATGAAAGTTCTATTCTGCCTGC
2201  CCTGAGGCTTAGTTACCATCATCTTCCACTTGATTTGAGACAATGCTTTG
2251  TGTATTGTGCGGTATTCCCAAAGGACACCAAAATGGCAAAGGAAAATCTT
2301  ATCGCTTTTTGGATGGCACATGGTTTTCTTTTATCGAAAGGAAATTTGGA
2351  GCTAGAGGATGTAGGTAATGAAGTATGGAATGAATTATACTTGAGGTCTT
2401  TCTTCCAAGAGATTGAAGTTGAATCTGGTAAAACTTATTTCAAGATGCAT
2451  GACCTCATCCATGATTTGGCTACATCTCTGTTTTCAGCAAACACATCAAG
2501  CAGCAATATTCGTGAAATAAATGCTAATTATGATGGATATATGATGTCGA
2551  TTGGTTTTGCTGAAGTGGTATCTTCTTACTCTCCTTCACTCTTGCAAAAG
2601  TTTGTCTCATTAAGGGTGCTTAATCTAAGAAACTCGAACCTAAATCAATT
2651  ACCATCTTCCATTGGAGATCTAGTACATTTAAGATACCTGGACTTGTCTG
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3001  TGAAGAAAGATAGCGATGCAAAAGAAGCTAATTTATCTGCTAAAGCAAAT
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3851  AACAGCCCTCACAACTTTAACAATTACTCAATGTCCAATAGTATTCAAGC
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3951  TATTTGACTCTATATGAGTGA
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Figure 6F

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1     ATGGCGGAAGCTTTTCTTCAAGTTCTGCTAGAAAATCTCACTTCTTTCAT
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101   TGTCGAGTGTGTTTTCCACAATTCAAGCTGTGCTTCAAGATGCTCAGGAG
151   AAGCAATTGAAGGACAAGGCAATTGAGAATTGGTTGCAGAAACTCAATTC
201   TGCTGCCTATGAAGTTGATGATATATTGGGCGAATGTAAAAATGAGGCAA
251   TAAGATTTGAGCAGTCTCGATTAGGGTTTTATCACCCAGGGATTATCAAT
301   TTCCGTCACAAAATTGGGAGAAGGATGAAAGAGATAATGGAGAAACTAGA
351   TGCAATATCTGAGGAAAGAAGGAAGTTTCATTTCCTTGAAAAAATTACAG
401   AGAGACAAGCTGCCGCTGCTACGCGTGAAACAGGTGTGAGTACTGAGTAA
451   TTGTAGCTTAGTTAATATTCAATTTGTTACCACATCATGTGTTCACCGTG
501   ATCTCTACAGTAGGATGGCAATGGGGCTGGGCGAGGTTGGAGGTGTGCAG
551   GTGTGTGGCGCAACCCCAACTTTGAGTCTACATAAGTAGGTACTTAAATT
601   TGTATAGAGTTGAACAAGTACAAACGCCTCCTACTTGGTGTCCTTATGCG
651   TATTATGTCACTTAGGATGCATGTGTCTACTTGTTCAACTTTATATGAGT
701   TTAAGTTCTACTTGTGCACACCCAAAGTTGGAGCGCGTAGATGTCAGTTG
751   ATACCAAGTTAAAAAGGCATATTTATGAATTATGCCTTTAAATTATGATT
801   CAATTTTGTATCAGTCTGTCCAAAATATGTTCTAGTGAAAGTGTTAAACT
851   TAGTCTGGATCTGCTATTGAAAGTGAATTTTTGTGGCACTAAACAATGCA
901   ATGGGTCTGGATTCATTTTTGCATTAACTTTTGTTTAGACGATTTTCTTT
951   ATCGAATTTTACTGTCTAAAATGGAAAAAGCAAAGAAATAAGAAGTATAC
1001  AGAGGCTGACTTCTTCATAGTATCTATCATATAAAAAAAAGCATTGATTA
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1101  GTTGGGAAGGATTTAGATACACGTGGATAGTATCTAGAAGTTTTTTAAAT
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1201  TGCAAGGCTTGGCGGGTCGAAATCTTTGCAAGTTTGTGTGGGTTTGCCCT
1251  GCACCACCCAATCTGCCATTCCTGTCTAAATGTTTGTTTTGTCTATAATT
1301  CTTGCTGACTCATTCTAATGAGCTCAATTGTAACAAATTCTTTGTGTCCA
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1401  GACAAAGAGGAGGATGAGATAGTGAAAATTCTGATAAACAATGTTAATGT
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1701  CGATACTTGCTTGTCTTAGATGATGTTTGGAATGATGATCTAGAAAAGTG
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1901  GCAACGCGCATTTGGGCAACAAAAAGAAGCAAATCCTAATCTAGTGGCCA
1951  TTGGAAAGGAGATTGTGAAGAAATGTGGTGGTGTGCCTTTAGCAGCCAAG
2001  ACTCTTGGTGGTCTTTTACGCTTCAAGAGAGAAGAGAGTGAATGGGAACA
2051  TGTGAGAGATAATGAGATTTGGAGTCTGCCTCAAGATGAAAGTTCTATTT
2101  TGCCTGCTCTAAGACTGAGTTATCATCACCTTCCACTTGATTTGAGACAA
2151  TGCTTTGCGTATTGTGCAGTATTCCCAAAGGACACCAAAATGATAAAGGA
2201  AAATCTCATTACTCTCTGGATGGCGCATGGTTTTCTTTTATCAAAGGGAA
2251  ACTTGGAGCTAGAGGATGTGGGTAATGAAGTATGGAATGAATTATACTTG
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2451  GTGTCCATTGGTTTCGCTGCAGTGGTGTCTTCTTACTCTCCTTCGCTCTT
2501  GAAAAAGTTTGTCTCGTTAAGGGTGCTTAATCTAAGTTACTCAAAACTTG
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2651  AAATCTTCAGACTCTTGATGTACATAATTGCTACTCACTTAATTGTTTGC
2701  CAAAACAAACAAGTAAACTTAGTAGTCTCCGACATCTTGTTGTTGATGGC
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2801  GACTCTAGGTTTCTTTATTGTGGGAAGCAAGAAAGGTTATCAACTTGGTG
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2951  TCTGCAATCTTTAAGCATGAGTTGGGATAACGATGGACCAAACAGATATG
3001  AATCCAAAGAAGTTAAAGTGCTTGAAGCACTCAAACCACACCCCAATCTG
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3151   AAAACTGCTTGTGCTTACCACCCTTTGGGGAGCTTCCTTGTCTAGAAAAT
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3251   TGTCCATTCTAGATTCTCCACAAGAAGAAGCTTTCCATCCCTGAAAAAAC
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3701   AGAAGGTTTAACTTCACTCACACAGTTGTTTGTTAAATACTGTAAGATGC
3751   TAAAATGTTTACCCGAGGGATTGCAGCACCTAACAGCCCTCACAAATTTA
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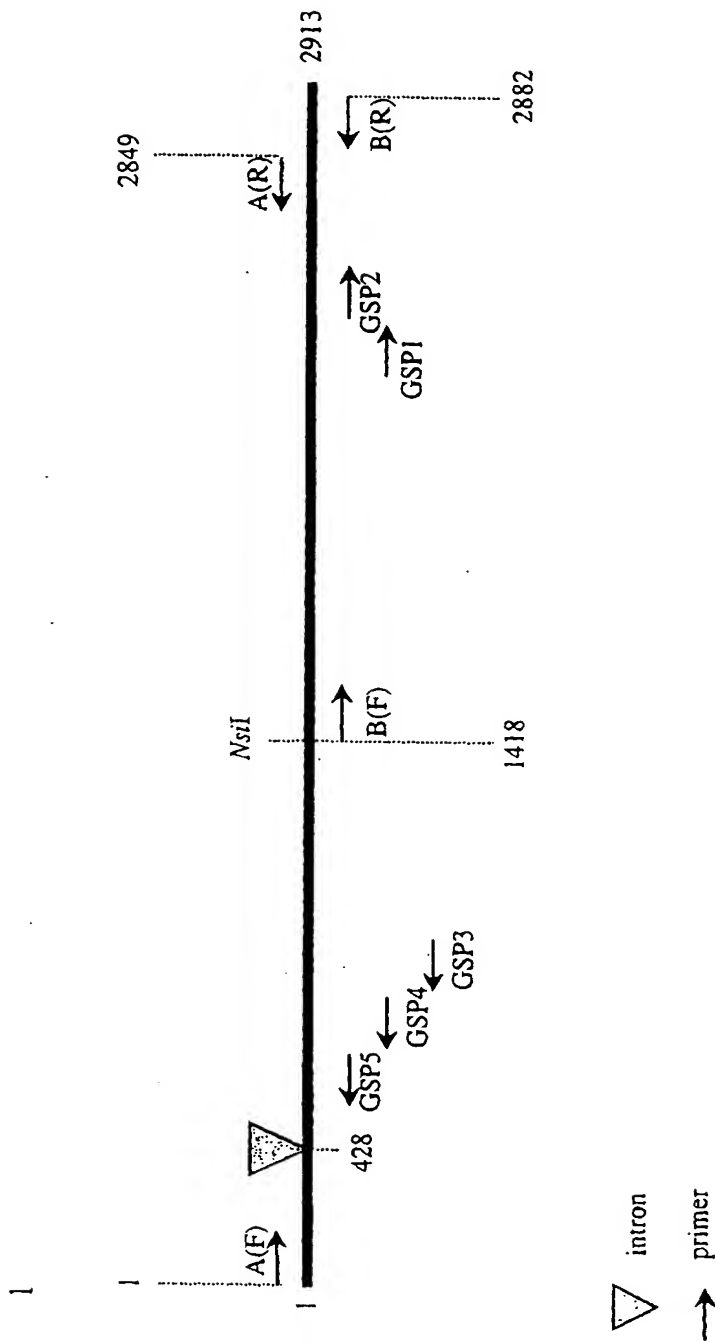
Figure 7

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A |  MAEAFIQVLLDNLTSFLKGELVLLFGFQDEFQRLSSMFSTIQAVLEDAQEKQLNN         55
  |  KPLENWLQKLNAATYEVDDILDEYKTKATRFSQSEYGRYHPKVIPFRHKVGKRMD         110
  |  QVMKKLKAIAEERKNFHLHEKIVERQAVRRETGSVLTEPQVYGRDKEKDEIVKIL         165


  |  INNVSDAQHLSVLpilgmggglgktt1aQMVFNDQRVTEHFHSKIWICVSEDFDEK       220
  |  RLIKAIVESIEGRPLLGEMDLAPLQKKLQELLNGkryllvlddvwNEDQQKWANL        275
  |  RAVLKVGASGAsvltttrLEKVGSIMGTLQPYELSNLSQEDCWLLFMQRAFGHQE        330
B |  EINPNLVAIGKEIVKKSGGVPLAAKTLGGILCFKREERAWEHVRDSPIWNLPQDE        385
  |  SSILPALRLSYHQLPLDLKQCFAYCAVFPKDAKMEKEKLISLWMAHGFLLSKGNM        440
  |  ELEDVGDEVWKELYLRSFFQEIEVKDGKTYFKmhdlihdlatSLFSANTSSSNIR        495
  |  EINKHS                                                        501

  |  YTHMMSIGFAEVVFFYTLPPLEK                                       524
  |  FISLRVLNLGDST.FNKLPSSIGD                                      547
  |  LVHLRYLNLYGSG.MRSLPKQLCK                                      570
  |  LQNLQTLDLQYCTKLCCLPKETSK                                      594
  |  LGSLRNLLLDGSQSLTCMPPRIGS                                      618
  |  LTCLKTLGQFVVGRKKGYQ                                           637
  |  LGELGNLNLYGSIKISHLERVKNDKDAKEANLSA                            671
  |  KGNLHSLSMSWNNFGPHIYESEEVKVLEALKP                              703
  |  HSNLTSLKIYGFRGIH.LPEWMNHSV                                    728
C |  LKNIVSILISNFRNCSCLPPFGD                                       751
  |  LPCLESLELHWGSAD                                               766
  |  VEYVEEVDIDVHSGFPTRIR                                          786
  |  FPSLRKLDIWDFGSLKGLLKKEGEEQ                                    812
  |  FPVLEEMIIHECPFLTLSSN                                          832
  |  LRALTSLRICYNKVATSFPEEMFKN                                     857
  |  LANLKYLTISRCNNLKELPTSLAS                                      881
  |  LNALKSLKIQLCCALESLPEEGLEG                                     906
  |  LSSLTELFVEHCNMLKCLPEGLQH                                      930
  |  LTTLTSLKIRGCPQLIKRCEKGIGEDWHK                                 959
  |  ISHIPNVNIYI                                                   970


   L..L..L.L..C..α..αP..    LRR consensus
        N
        S
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Figure 8
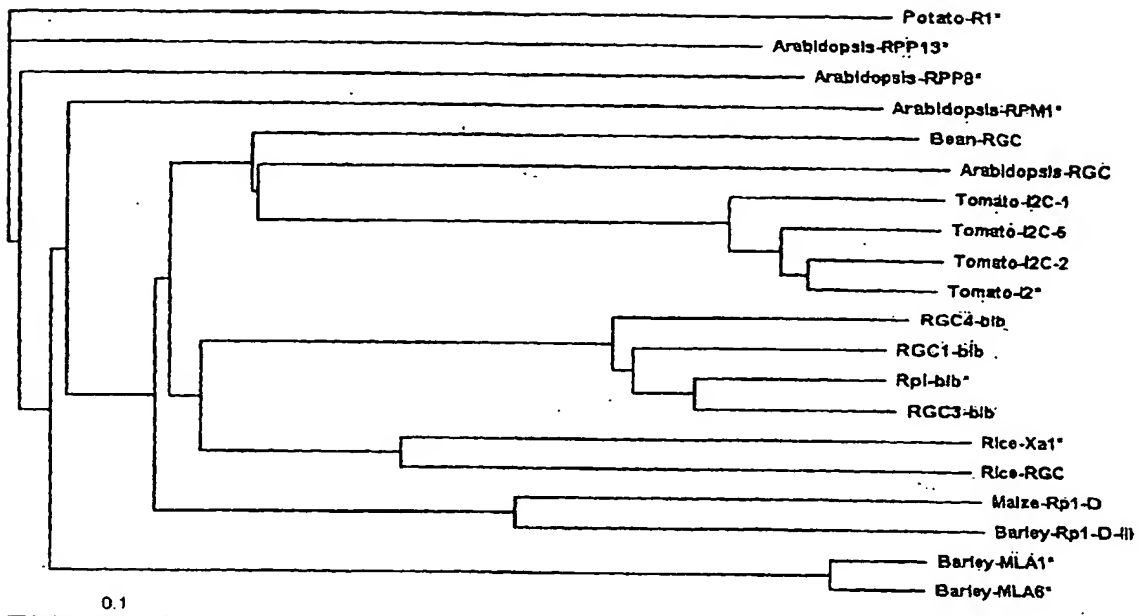
Figure 9

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RGC3-blb        V                                            D              60
RGC1-blb      L      E     F IQ   G V    EK KK     M              KY AIK     60
RGC4-blb      L      E       IGDK   I    EK CEK  V         Q      KD AI      60

Rpi-blb    WLQKLNAATYEVDDILDEYKTKATRFSQSEYGRYHPKVIPFRHKVGKRMDQVMKKLKAIA       120
RGC3-blb                         L                              N           120
RGC1-blb         V A         DC E A  K AVL    RT T CY      KEM E D          120
RGC4-blb         S A         G C NE I  E  RL F   GI N    IR KEI E  D    S   120

Rpi-blb    EERKNFHLHEKIVERQAVR--RETG-----------------------------------       143
RGC3-blb        Q   I    AT--    -----------------------------------       143
RGC1-blb      R    D R I    A -- Q   ----------------------------------     143
RGC4-blb      RK   FL   T    AAAT   VGWQWGWARLEYKRLLLGVLMRIMSLRMHVSTCSTL     180

Rpi-blb    ------------------SVLTEPQVYGRDKEKDEIVKILINNVSDAQHLSVLpilgmggl       186
RGC3-blb    ------------------                                 K             186
RGC1-blb    ------------------F     K    E  E           YSEEVP              186
RGC4-blb    YEFKFYLCTPKVGARRCF      K         E         NV EE  P F   I      240


Rpi-blb    gkttlaQMVFNDQRVTEHFHSKIWICVSEDFDEKRLIKAIVESIEGRPLLGEMDLAPLQK       246
RGC3-blb          S       R  YP    D                  KS S-D                245
RGC1-blb                 I    NL  V    D                KS G-D              245
RGC4-blb              I  E  K  NP  V    D         T IGN  -  SSPHVE    SF     299

Rpi-blb    KLQELLNGkryllvlddvwNEDQQKWANLRAVLKVGASGAsvltttrLEKVGSIMGTLQP       306
RGC3-blb          F              H               F                          305
RGC1-blb          F              E  D        I      I I        I       L    305
RGC4-blb                      D LE   K       T   R   I A                    359

Rpi-blb    YELSNLSQEDCWLLFMQRAFGHQEEINPNLVAIGKEIVKKSGgvplaaktlggILCFKRE       366
RGC3-blb           P   F                         C              R           365
RGC1-blb    Q           K    C  T TS K ME        C.            L R          365
RGC4-blb    H       PH SL        Q K A            C             L R         419

Rpi-blb    ERAWEHVRDSPIWNLPQDESSILPALRLSYHQLPLDLKQCFAYCAVFPKDAKMEKEKLIS       426
RGC3-blb       E                       H     R    V         T  A   N    A   425
RGC1-blb    SE         E         N V        H     R          T I    Y   A   425
RGC4-blb    SE       NE  S                  H     R          T I    N   T   479

Rpi-blb    LWMAHGFLLSKGNMELEDVGDEVWKELYLRSFFQEIEVKDGKTYFKmhdlihdlatSLFS       486
RGC3-blb    F            L      N   N             ES                 M      485
RGC1-blb             S            N   N            S          I             485
RGC4-blb                   L      N   N           A SN     I                539

Rpi-blb    ANTSSSNIREINKH----------GYTHMMSIGFAEVVFFYTLPPLEKFISLRVLNLGDS       536
RGC3-blb                AN----------YDGY      SS SPSL Q  V         RN       535
RGC1-blb    SA RS   Q  VKDDEDMMFIVTN KD     S  SS SPSLFKR V          SN     545
RGC4-blb    SA CG      VK----------D K TV    A  SS SPSL K  V          SY    589

Rpi-blb    TFNKLPSSIGDLVHLRYLNLYG-SGMRSLPKQLCKLQNLQTLDLQYCTKLCCLPKETSKL       595
RGC3-blb    NL Q           D S NFRI N    R          H DS S       Q         595
RGC1-blb    E EQ      V        D S -NKIC   R          YN QS S      Q        604
RGC4-blb    KLEQ          L    D SC-NNF    ER         VHN YS N     Q        648

Rpi-blb    GSLRNLLLDGSQSLTCMPPRIGSLTCLKTLGQFVVGRKKGYQLGELGNLNLYGSIKISHL       655
RGC3-blb              -C   ST     L      S SC   I KR        K         S TK  654
RGC1-blb    C     V H-CP  S      L          Y    ER        R    R A S T     663
RGC4-blb    S   H VV  -CP  ST     L          F I  S         K     C   S T   707

Rpi-blb    ERVKNDKDAKEANLSAKGNLHSLSMSWNNFGPHIYESEEVKVLEALKPHSNLTSLKIYGF       715
RGC3-blb    D   K S        A       CL    DLD K R D ---E            KY E N   711
RGC1-blb            ME       A           D--R NR               P  KY E ID   721
RGC4-blb          T  -       A  Q        D D  NR   K            P  KY E IA   766
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76

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Rpi-blb   ┌GIHLP⌐WMNHSVLKNIVSILISNFRNCSCLPPFGDLPCLESLELHWGSADVEYVEEVDI    775
RGC3-blb  G   R  D   Q      V    R RGCE           E         T        DN--    769
RGC1-blb  C FC  D            V      GCE           E         QD  VE    DS--    779
RGC4-blb  G FRF S I      EKVI VR KSCK  L          E     N   QN  E      D--    824

Rpi-blb   DVHSGFPTRIRFPSLRKLDIWDFCSLKGLLKKEGEEQFPVLEEMIIHECPFLTLS-----    830
RGC3-blb  -  P -----          V    SN          K            TFYW  MFVIPTLSSV  823
RGC1-blb  ---- L  R           H GG CN     QRMK A            K SD  MFVFPTLSSV  835
RGC4-blb       R S  RS      K  R  F R        M E     K M    A LY  LFVFPTLSSV  884

Rpi-blb   ----------------SNLRALTSLRICYNKVATSFPEEMFKNLANLKYLTISRCNNLK    873
RGC3-blb  KTLKVI-ATDATVLRSI        D SN VE    L        S        N  FFR         882
RGC1-blb  KKLEIWGEADAGGLSSI    ST   K FS HTV  LL            E I  SV FLE         895
RGC4-blb  KKLEVHGNTNTRGLSSI .  ST     GA YR   L        TS T  EF SFFDFK         944

Rpi-blb   ELPTSLASLNALKSLKICLCCALESLPEEGLEGLSSLTELFVEHCNMLKCLPEGLQHLTT    933
RGC3-blb              FEF N        VK  T      S SN M               A          942
RGC1-blb         N  C D RY Y                                                  955
RGC4-blb  D      T    R Q ES DS   F  Q      T   Q  KY K             A         1004

Rpi-blb   LTSLKIRGCPQLIKRCEKGIGEDWHKISHIPNVNIYI                         970
RGC3-blb    T  T TQ  IVF    R       A   YLTL E                          979
RGC1-blb                                                                992
RGC4-blb    N GVS   EVE    D E      A    LD H-                          1040
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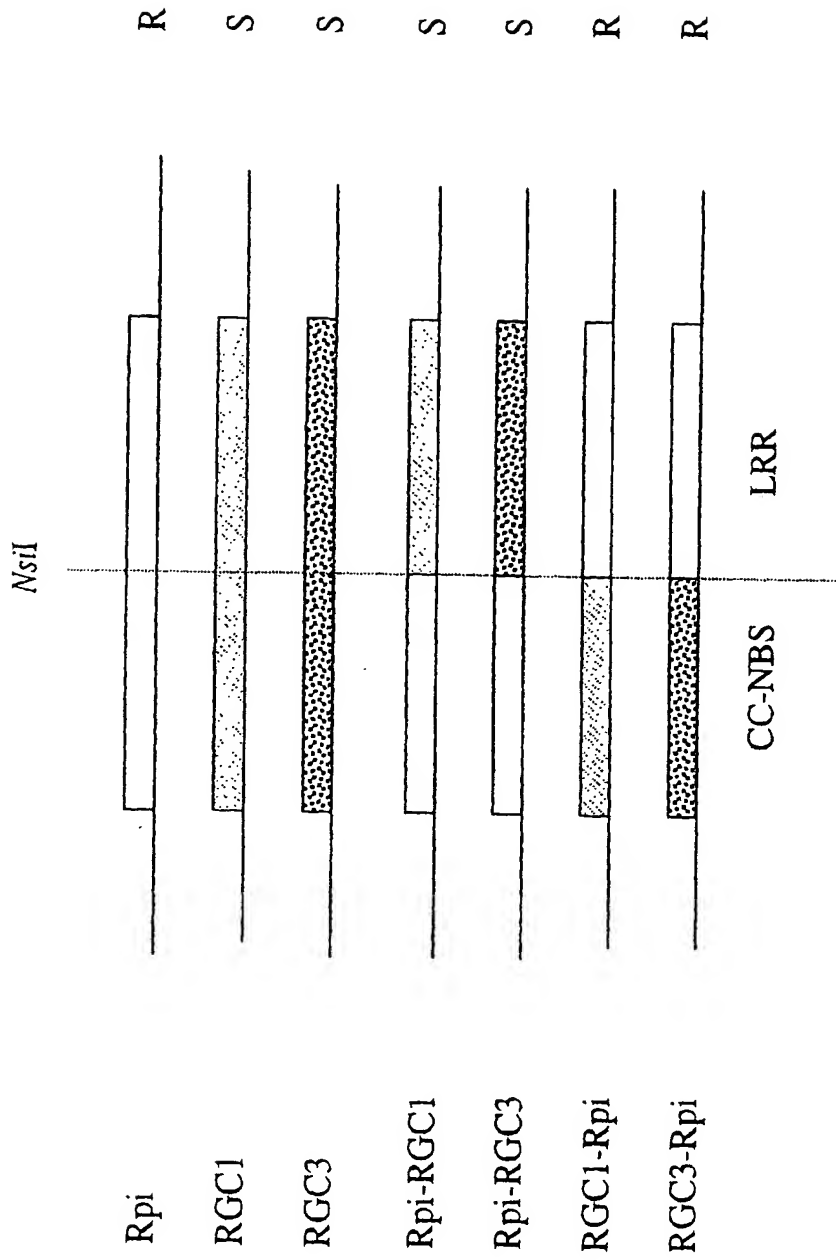
Figure 10

Figure 11

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number

EP 02 07 5565

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DATABASE EMBL 'Online! EMBL; 5 September 2001 (2001-09-05) PAN Q. ET AL.: "Lycopersicon esculentum isolate Q194 nucleotide binding region of resistance-like gene, partial sequence" Database accession no. AF404480 XP002206417	1-23	C07K14/415 C12N15/82 C07K16/16 G01N33/50 C12N5/10 A01H1/04
Y	* abstract * -& PAN Q. ET AL.: "Comparative genetics of nucleotide binding site-leucin rich repeat resistance gene homologs in the genomes of two dicotyledons: tomato and arabidopsis" GENETICS, vol. 155, no. 1, 2000, pages 309-322, XP002207023 ---	24-31	
X	DATABASE SWISSPROT 'Online! EBI; 1 December 2001 (2001-12-01) SASAKI T. ET AL.: "Putative NBS-LRR type resistance protein" Database accession no. Q94J89 XP002206418	1-23	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C12N C07K
Y	* abstract * ---	24-31	

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INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	22 July 2002	Marinoni, J-C

EPO FORM 1503 03.82 (P04C07)

	European Patent Office	INCOMPLETE SEARCH SHEET C	Application Number EP 02 07 5565

Claim(s) searched completely:
    –

Claim(s) searched incompletely:
        32

Reason for the limitation of the search (non-patentable invention(s)):

Article 53 (b) EPC – Plant variety

                    ––––––––––––––––––––

Further limitation of the search

Claim(s) searched completely:
    –

Claim(s) searched incompletely:
        1–32 all partially

Reason for the limitation of the search:

Present claims 1-4 and 6 relate to a nucleic acid defined by reference to
a desirable characteristic or property, namely that it is identifiable by
phylogenetic tree analysis as corresponding to the Rpi-blb, RGC1-blb,
RGC2-blb and RGC4-blb gene cluster.
The claims cover all nucleic having this characteristic or property,
whereas the application provides support within the meaning of Article 84
EPC and/or disclosure within the meaning of Article 83 EPC for only a
very limited number of such nucleic acids. Moreover, due to the purpose
itself of the tree analysis, virtually any known late-blight LRR
resistance gene, but also any gene whatever the extent of its homology to
the genes of the invention and whatever its function, can be retrieved.
In the present case, the claims so lack support, and the application so
lacks disclosure, that a meaningful search over the whole of the claimed
scope is impossible. Independent of the above reasoning, the claims also
lack clarity (Article 84 EPC). This lack of clarity is such as to render
a meaningful search over the whole of the claimed scope impossible.
The additonal provisions of claims 2-4 and 6 are not considered as being
true technical feature that would enable the skilled person to define
properly the nucleic acids for which protection is sought (Article 84
EPC) and to put the invention into practice without undue burden (Article
83 EPC).

Additionally, claim 15 tries to define a proteinaceous substance by
reference to a result to be achieved, namely that it provides at least
partial resistance to oomycete infection, whereas only a very limited
number of such proteinaceous substances has been disclosed in the
application as filed.

Consequently, the search has been carried out for those parts of the
claims which appear to be clear, supported and disclosed, namely those
parts relating to the proteins having the sequences of SEQ ID No. 41 to
44 and the nucleic acids encoding them corresponding to the Rpi-blb,

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Office

**INCOMPLETE SEARCH
SHEET C**

Application Number

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RGC1-b1b, RGC2-b1b and RGC4-b1b genes respectively, or fragments thereof, and to sequences sharing at least 50% identity with the sequences disclosed in the specification (see page 6, lines 5-8).

Consequently, all claims referring back directly or indirectly to the nucleic acids of claims 1-6 have also been searched partially.

Additionally again, claims 18 and 20 are directed to molecules binding either the proteins of claims 15-18 or the nucleic acid of claims 1-6, whereas the application provides support and disclosure only for a limited number of such molecules i.e. antibodies on one hand and primer/probes on the other hand. The search has been restricted to antibodies and primers/probes respectively. All claims referring back directly or indirectly to claims 18 and/or 20 were partially searched too.

Additionally again, claim 32 is directed to a plant that does not necessarily contain the gene(s) of the invention and could be a plant that has been obtained through traditional breeding methods, which are excluded from patentability under Article 53(b) EPC.

	PARTIAL EUROPEAN SEARCH REPORT		Application Number
European Patent Office			EP 02 07 5565

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE EMBL 'Online! EMBL; 8 June 2001 (2001-06-08) BOUGRI O. ET AL.: "Generations of ESTs from dormant potato tubers" Database accession no. BG890602 XP002206419 * abstract *	1-23	
D,Y	VAN DER BIEZEN E A ET AL: "THE NB-ARC DOMAIN: A NOVEL SIGNALLING MOTIF SHARED BY PLANT RESISTANCE GENE PRODUCTS AND REGULATORS OF CELL DEATH IN ANIMALS" CURRENT BIOLOGY, CURRENT SCIENCE,, GB, vol. 8, no. 7, 26 March 1998 (1998-03-26), pages R226-R227, XP000924862 ISSN: 0960-9822 * the whole document *	1-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
Y	LEISTER D ET AL: "A PCR-BASED APPROACH FOR ISOLATING PATHOGEN RESISTANCE GENES FROM POTATO WITH POTENTIAL FOR WIDE APPLICATON IN PLANTS" NATURE GENETICS, NEW YORK, NY, US, vol. 14, December 1996 (1996-12), pages 421-429, XP000964717 ISSN: 1061-4036 * the whole document *	1-31	
A	VAN DER BIEZEN ERIC ET AL: "Plant disease-resistance proteins and the gene-for-gene concept" TIBS TRENDS IN BIOCHEMICAL SCIENCES, ELSEVIER PUBLICATION, CAMBRIDGE, EN, vol. 23, no. 12, December 1998 (1998-12), pages 454-456, XP002158209 ISSN: 0968-0004		

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EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 02 07 5565

	DOCUMENTS CONSIDERED TO BE RELEVANT		CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	DONG F ET AL: "Development and applications of a set of chromosome-specific cytogenetic DNA markers in potato." THEORETICAL AND APPLIED GENETICS, vol. 101, no. 7, November 2000 (2000-11), pages 1001-1007, XP001087853 ISSN: 0040-5752 ---		
A	ELLIS JEFF ET AL: "Structure, function and evolution of plant disease resistance genes." CURRENT OPINION IN PLANT BIOLOGY, vol. 3, no. 4, August 2000 (2000-08), pages 278-284, XP002206415 ISSN: 1369-5266 ---		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	YOUNG NEVIN DALE: "The genetic architecture of resistance." CURRENT OPINION IN PLANT BIOLOGY, vol. 3, no. 4, August 2000 (2000-08), pages 285-290, XP002206416 ISSN: 1369-5266 ---		
A	OBERHAGEMANN P ET AL: "A GENETIC ANALYSIS OF QUANTITATIVE RESISTANCE TO LATE BLIGHT IN PATATO: TOWARDS MARKER-ASSISTED SELECTION" MOLECULAR BREEDING: NEW STRATEGIES IN PLANT IMPROVEMENT, KLUWER ACADEMIC PUBLISHERS, NL, vol. 5, no. 5, 1999, pages 399-415, XP001079515 ISSN: 1380-3743 --- -/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 02 07 5565

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with Indication, where appropriate, of relevant passages	Relevant to claim	
A	THIEME R ET AL: "PRODUCTION OF SOMATIC HYBRIDS BETWEEN S.TUBEROSUM L. AND LATE BLIGHT RESISTANT MEXICAN WILD POTATO SPECIES" EUPHYTICA, KLUWER ACADEMIC PRESS, AMSTERDAM, NL, vol. 97, no. 2, 1997, pages 189-200, XP002912898 ISSN: 0014-2336		

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

European Patent
Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☒ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office	LACK OF UNITY OF INVENTION SHEET B	Application Number EP 02 07 5565

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-32 all partially

   The RPI-blb gene or RGC2-blb gene having the sequences of SEQ ID No. 35 and 36, the SEQ ID No. 37, all three sequences conferring late-blight resistance in Solanaceae, the protein encoded thereby having the sequence of SEQ ID No. 41, methods and plants related to said gene, etc...

2. Claims: 1-32 all partially

   The RGC1-blb, RGC3-blb and RGC4-blb genes of SEQ ID No. 38, 39, and 40, which do not confer late-blight resistance in Solanaceae, the protein encoded thereby having the sequences of SEQ ID No. 43, 42, and 44 respectively, methods and plants related to said gene, etc...